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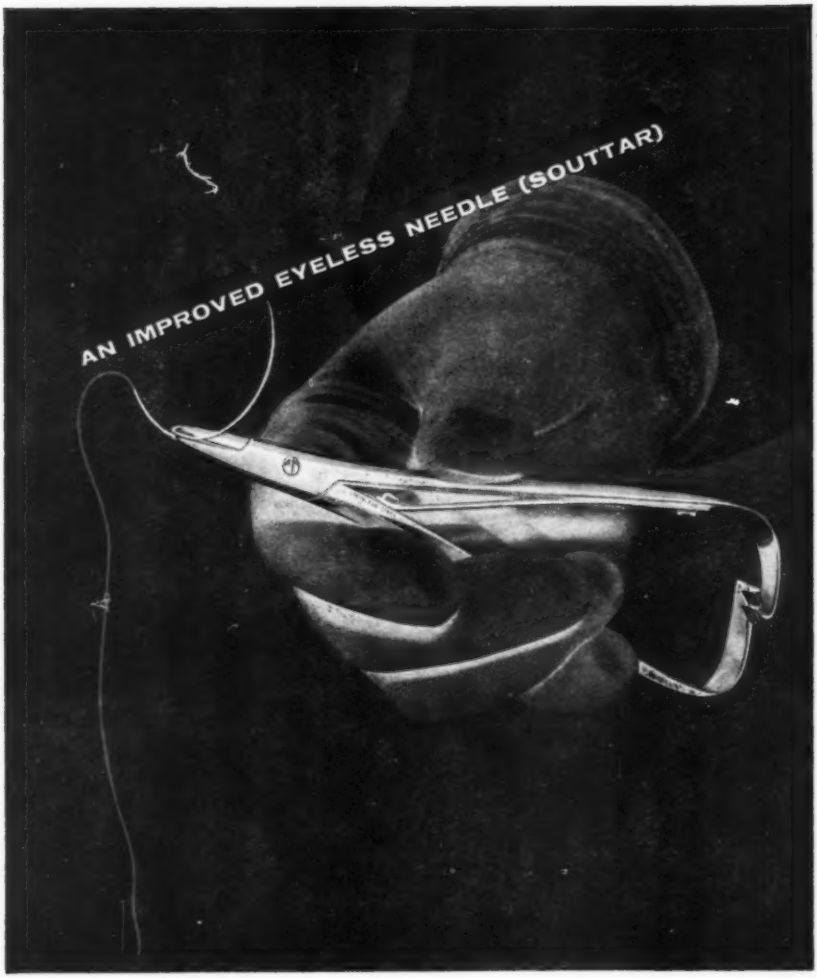

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The Journal of
Obstetrics and Gynaecology of the British Empire

VOL. LXV, No. 6 NEW SERIES DECEMBER 1958

AGE AND HUMAN REPRODUCTION

BY

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DECLINE begins when maturation is complete. This physiological truth has received little attention in medical research, possibly as a result of the current pre-occupation with the problems of senility. Yet athletes who depend on speed are well aware that a man can be too old at thirty; and certain intellectual abilities are said to decline slowly after about 25 (Wechsler, 1944). Welford (1951) states that "Recent research on changes with age in experimental skills have shown that some of these changes can be detected as early as the late twenties . . .". In everyday life, early biological degeneration is of little practical consequence because social maturation and accumulated experience continue to benefit the individual at least until late middle age. These general patterns of maturation and decline at varying rates are influenced by the social context in which the individual lives.

In this paper the patterns are illustrated and discussed in relation to human reproduction. Marriage and childbearing involve, for women between the ages of about 16 and 45, tests of social and mental ability, and of physical stamina. The problems of ageing in this context are medically and socially important, especially in a culture where it is customary to delay childbearing for some years beyond the attainment of physical maturity, and to have many fewer children than the biological limit.

Obviously the problem has to be viewed from many angles and this paper will be divided into two parts; first, the general significance of age differences in primiparae, and, second, a description of the effects of age on various aspects of reproduction.

SOURCES OF DATA

The data presented in this paper are derived chiefly from records of single first births to married women resident in the city of Aberdeen. With a population of 186,000, Aberdeen is an industrial city, a University centre and the commercial capital of an extensive and isolated agricultural region. Findings in a survey of age and reproduction in Aberdeen are not likely to differ materially from those to be expected in urban Scotland as a whole.

THE GENERAL SIGNIFICANCE OF AGE DIFFERENCES

The interpretation of trends with age in clinical statistics is complicated by the fact that women in different age groups are by no means comparable in other respects.

Parity. The most obvious complication is that of parity. The proportion of primiparae falls from about 90 per cent in mothers aged under 20 to about 15 per cent in those aged 40 or more; and the proportion of those with 4 or more previous children rises from almost nil to more than one-third.

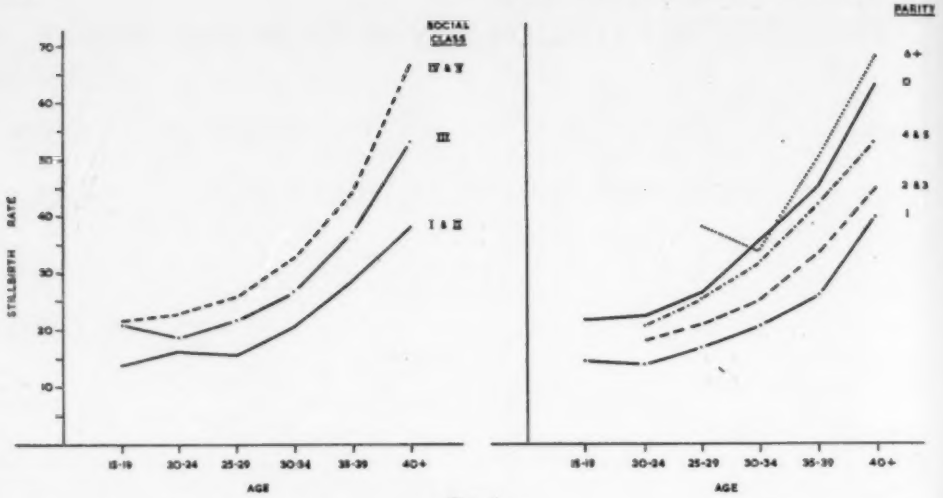

FIG. 1

Stillbirth rates, Scotland 1950–56, by maternal age and husband's social class and by maternal age and parity.

The right-hand side of Figure 1 shows the stillbirth rates in Scotland by maternal age in each parity. Roughly similar trends of increasing rates with age appear in all parities; but in each age group the rates are higher for first births (parity-O) than for all subsequent births up to the sixth. Women having second babies have the lowest stillbirth rates, in each age-group. Obviously, therefore, the parity composition of any population for study is liable to influence trends with age. For example, the stillbirth rate (all parities together) for women aged under 20 is 20·5, compared with 19·1 for women aged 20–24; the slight fall is mainly due to the fact that the great majority of women aged under 20 are primiparae. Again, a hospital population including a relatively high proportion of high parity women is liable to have a high stillbirth rate at ages over 35, for this reason alone.

*Social Class.** The left-hand side of Figure 1 shows the stillbirth rates in Scotland (all parities) by maternal age and husband's social class. Once again, the rates in each class rise with age, especially after the age of 30; in each age group the lowest rates are found in Social Classes I and II (wives of professional men, business managers and the like).

The nature of the relationship between social class and age at a first maternity is well known. Women from the educated classes usually postpone marriage and childbearing until economic stability has been attained, and both are deliberately planned as a rule. Among the poor and ill-educated, lack of planning is much more characteristic. Thus, of women having a first baby before the age of 20, who are mostly in the lower social classes, no less than 65 per cent marry after conception. Pre-nuptial conception no doubt signifies in part ignorance of sexual physiology and contraceptive technique, but where rates are very high, as in Social Classes IV and V (semi-skilled and unskilled working classes), there may also be a less strong social disapproval of pre-marital intercourse such as probably acts as a deterrent in Social Classes I and II (Scott, Illsley and Biles, 1956; Thompson, 1956). Baird (1946) has shown that women who have a pre-nuptial conception generally go on to have a larger family more quickly than women who marry before conception.

To simplify analysis and discussion, the remainder of this paper will be concerned almost

* The Social classification used is that of the Registrar-General (General Register Office, 1951).

entirely with married primiparae having single births. Primiparae, in addition to being the largest and most important parity group, have an inherent advantage for present purposes, in that about 90 per cent of Aberdeen primiparae receive antenatal care and are delivered in hospital as booked cases; hospital records for primiparae are therefore little biassed by selection.

The relationship between age and social class for 5,339 married primiparae delivered in Aberdeen between 1949 and 1954 is shown in Figure 2. Relatively few mothers aged under 25

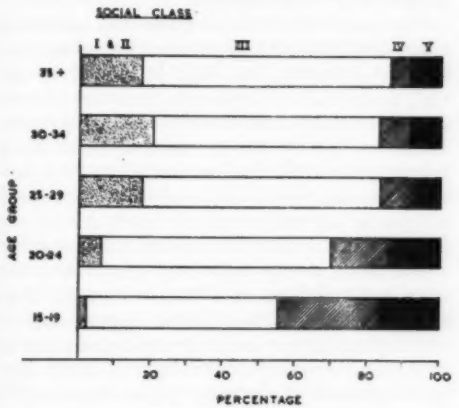

FIG. 2

The relationship between maternal age at first delivery and husband's social class.

are in the professional and managerial groups (Social Classes I and II); conversely, relatively few aged over 25 are in the semi- and unskilled working classes (Social Classes IV and V).

Physique and Health. In the upper social classes women are generally better grown than in the lower social classes (Baird, 1952a; Illsley, 1955) and this is reflected in the distribution of heights in the different age groups shown in Figure 3. Less than 20 per cent of women having their first baby before the age of 20 are 5 feet 4 inches or more (tall) and almost 30 per cent are less than 5 feet 1 inch (small). In the age group 30–34, 35 per cent are tall and only 17 per cent small. Growth usually ceases about age 18, so these trends cannot be explained in terms of immaturity. Primiparae aged 35 and

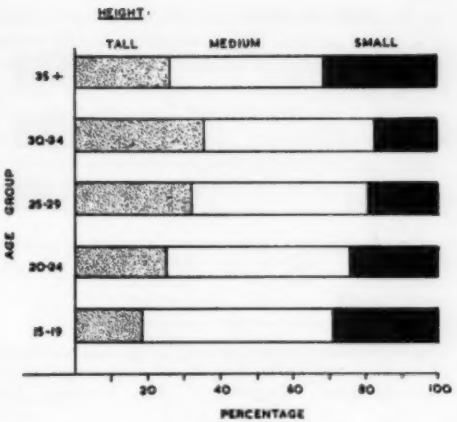

FIG. 3

The relationship between maternal age at first delivery and height. (Tall=5 feet 4 inches or more, small=under 5 feet 1 inch.)

over are generally smaller than those in the immediately preceding age groups; but this small group is a complicated mixture probably containing a high proportion of relatively infertile women and its characteristics cannot properly be judged on the same basis as other age groups.

Height and general health are correlated, taller (and usually older) primiparae being generally of better physique and in better health than the smaller, younger women. For some years, maternity hospital patients in Aberdeen have been graded in terms of general physical health. The grading is carried out at the first clinic attendance by a senior clinician and the process has been standardized as far as possible. Figure 4 shows the relationship between height and physical grade among 4,386 primiparae examined during the years 1950–54. About 86 per cent of the tall women were graded as "very good" or "good", compared with only 50 per cent of small women; only 2·5 per cent of tall women were graded as "poor" or "very poor", compared with 10 per cent of small women. The clinical gradings are, of course, subjective, but the fact that many of the small women are stunted has received objective confirmation from X-ray pelvimetry (Bernard,

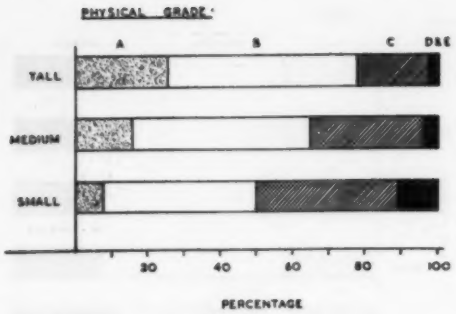

FIG. 4

The relationship between maternal height and assessment of physique and health at first visit to antenatal clinic. (A=very good, B=good, C=fair, D=poor, and E=very poor.)

1952). There is more flattening of the pelvic brim among shorter women, especially those in poor physical health, than among tall women and those in good health. This flattening is a deformity, less only in degree than that seen in rickets.

Education. The proportion of women remaining at school after the minimum leaving age rises from about 7 per cent in those who have their first baby under the age of 20 to about 28 per cent in those who have their first baby between the ages of 30–34.

To summarize, many of the younger primiparae live in poor social conditions, are stunted and in poor physical health, and have the minimum amount of school education; among them, a first pregnancy is often a sudden complication of early maturity rather than a planned undertaking. Towards the other end of the age scale are those women who postpone childbearing for many years after physical maturity is reached, in order to attain and maintain high socio-economic standards. They are taller and healthier and better educated.

The analysis which follows indicates that reproduction is most efficient, in physiological terms, when it begins soon after the attainment of physical maturity; delay in the use of the reproductive functions is associated with a progressive deterioration of physiological efficiency. But this pattern is complicated and in part obscured by the opposing social trends. The biological advantages of youth are offset, and may be outweighed in some respects, by such consequences of a poor social environment as sub-normal growth, impaired general health and poor education; conversely, the physiological disadvantages of postponing marriage and childbearing in the interests of economic advancement are to some extent offset by the fact that those who do so are usually well-grown and healthy and may have acquired a fuller sense of responsibility and extra social skills from their longer period of education.

The social connotation of age may have even more direct clinical implications. The obstetrical team in Aberdeen has been impressed by the high proportion of women from the poorer classes who look much older than their years. Thus, it is by no means uncommon to see a primigravida of 22 who has lost all the "bloom" of youth and who could easily be taken for a woman in her late twenties or early thirties. By the time such women have borne 4 or 5 children —and many do so within ten years—they are worn out and look as if they were aged 40 or more. Whether this clinical appearance of physical ageing is associated with commensurate physiological ageing must remain in doubt until we have means of assessing "physiological age"; but there seems every reason to believe that such an association exists.

THE EFFECT OF AGE ON REPRODUCTIVE PROCESSES

Conception. National statistics for England and Wales show a steady increase of childlessness with rising age at marriage. This trend, in the data for recent decades at all events, must be due in part to voluntary childlessness, but a similar trend is present in data referring to women married between 1861 and 1871 (Registrar-General, 1917) when the practice of birth control must have been uncommon and the methods used inefficient. McKeown and Record (195.) showed that the proportion of women becoming pregnant again within two years of the birth of their first baby diminished with increasing age from 25 per cent in those under 25 to 11 per cent in those aged 35 or

more; but, since women who delay marriage and childbearing until the thirties tend to limit their families voluntarily, the effect of biological infertility, if any, is obscured. In a recent American investigation, Guttmacher (1956) showed that when contraception is not practised "There is a detrimental effect of increasing age on fertility—it raises the primary sterility rate in the female and even lowers the likelihood for conception in women with previously proved fertility". The reasons are no doubt complex; they are certainly obscure.

Pregnancy. The incidence of pre-eclamptic toxaemia, the commonest serious complication of a first pregnancy, appears to be little affected by age. Nelson (1955) has shown that severe pre-eclampsia, characterized by a rise in late pregnancy of diastolic blood pressure to 90 mm. Hg or more on at least two occasions with more than a trace of protein in the urine, has almost the same incidence in all age groups. The incidence of mild pre-eclamptic toxaemia, which was diagnosed solely on a rise in blood pressure, shows a sharp rise in primigravidae over the age of 30. This rise may more truly indicate hypertensive disease than a true increase of pre-eclampsia.

A recent unpublished study of Aberdeen clinical records shows that the incidence of placenta praevia and of ectopic pregnancy in primigravidae rises steadily with age, suggesting that embedding of the ovum in an abnormal site becomes more common as age increases.

There is little information about the effect of age on such common minor disabilities of pregnancy as nausea and vomiting, heartburn, cramps and general lassitude. But, our clinical impression is that those primigravidae who "have never felt better" during pregnancy are mostly young, in spite of the fact that many of these live in poor housing and remain in paid employment until late pregnancy.

Foetal and Infant Mortality. Although clear-cut trends with age in many of the clinical disorders of pregnancy have not been demonstrated, it is easy to show that age has a marked effect upon the chance of survival of the foetus. In general, stillbirth rates rise steadily with maternal age after 20; and this is true for all causes of death except foetal malformations, which tend to decline with age, at least in primiparae (Baird, Walker and Thomson, 1954). For example, the following figures show, for primiparae, the stillbirth rates attributed to severe pre-eclampsia, and the stillbirth rates in cases of severe pre-eclampsia, compared with the incidence of severe pre-eclampsia (Nelson, 1955; Baird, Walker and Thomson, 1954).

Age	Stillbirths Attributed to Pre-eclampsia Per 1,000 First Births	Stillbirths Per 1,000 First Maternities with Severe Pre-eclampsia	Incidence of Severe Pre-eclampsia Per 100 First Maternities
Under 20 ..	7·5	92	4·4
20–24 ..	2·8	27	4·2
25–29 ..	4·2	65	5·4
30–34 ..	9·2	179	5·2
35 and over	19·0	290	4·9

The stillbirth rates are lowest in the age group 20–24, being relatively high in women aged under 20 and rising steeply with increasing age after 25. The youngest primiparae come mostly from the poorest social classes and for this reason the vitality of the foetus is impaired and it dies more easily from the effect of pre-eclampsia. Similar considerations cannot account for the high stillbirth rates after the age of 25, and it must be assumed that foetal vitality is depressed as part of the change associated with the ageing process in the mother. The trends in the stillbirth rates are not accounted for by variations in the incidence of pre-eclampsia in the different age-groups, and there is no reason to believe that the severity of the condition differs much by age.

An interesting extension of this line of reasoning can be derived from a study of the effect of multiple pregnancy on the total stillbirth rate. Morris and Heady (1955) have shown that in single births the rate is fairly steady in age groups up to 25–29, and then begins to rise, but in multiple births the youngest mothers are at a very great disadvantage. The data for these young women refer to all parities and include not only young primiparae but also women who have had several children in rapid succession

at a relatively early age, a phenomenon which is almost confined to the poorer classes. Figure 5, based on the data of Morris and Heady, shows that the physiological inefficiency which

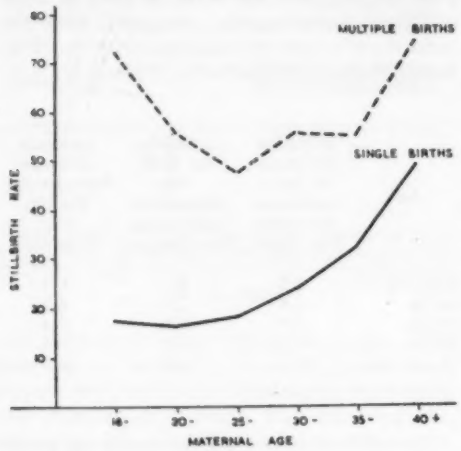

FIG. 5

Variation of stillbirth rate with maternal age for all births in England and Wales in 1949. (From Morris and Heady, 1955.)

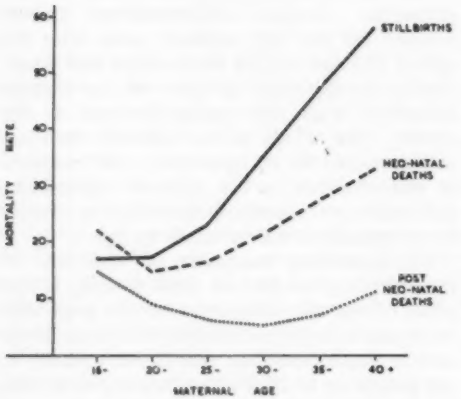

FIG. 6

Variation of stillbirth rate, neonatal death rate and post-neonatal death rate with maternal age for all first, single births, England and Wales, 1949. (From Morris and Heady, 1955.)

is associated with poor upbringing and environment and appears in an excess of stillbirths, even in single births, to women under 20 is much more obvious when multiple pregnancy increases the physiological stress.

Figure 6, also adapted from Morris and Heady (1955), shows the stillbirth, neonatal and post-neonatal death rates in primiparae by age. In the case of a stillbirth, the mother's age is obviously of prime importance since the rates rise steeply with age, especially after twenty-five years. The stillbirth rates do not increase much before the age of 25, probably because the rates in the youngest groups are higher than they need be on account of the poor health and physique and poor social background of many of the very young mothers. The direct influence of maternal age on the vitality of the baby after one month is slight and environmental influences (mainly infections) predominate. The effect of social selection is such that post-neonatal death rates fall with rising maternal age, up to about 35. Very young mothers tend to provide low standards of child care in keeping with their poor environment, since most of them come from the lowest social group. The trends have little to do with age as a biological characteristic, but are almost entirely dictated by the social background from which the several age groups are derived. The pattern of neonatal death rates is intermediate between that of the stillbirth rate and post-neonatal death rate. The rate is lower in the age group 20–24 than at 16–19, as a result of social class selection; in the older age groups, the effect of age *per se* predominates, as for stillbirths.

Labour. The effect of maternal age on first labours has been shown by Baird (1952b). Figure 7 shows the incidence of various types of delivery by age in 1,792 booked married primiparae delivered in the years 1949–50.* The incidence of spontaneous delivery in less than 24 hours fell from 80 per cent in the women

* Baird's data have not been brought up to date for this paper because the trends shown have been accentuated in recent years, when operative delivery has been adopted much more frequently for foetal distress, especially in elderly primigravidae. In the period covered by Figure 7, Caesarean section was performed almost exclusively for difficult labour.

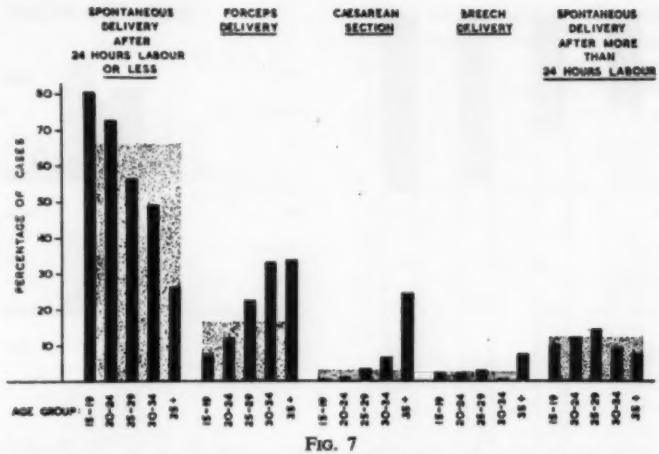

FIG. 7

Type of labour in relation to maternal age at first delivery in a series of Aberdeen primiparae in the years 1949 and 1950. The stippled area represents the mean in each group. (From Baird, 1952b.)

under 20, to 26 per cent in those of 35 years or over; the incidence of labour lasting more than 48 hours rose from 2 per cent in the youngest to 8 per cent in the oldest age group. Forceps delivery rose steadily with increasing age and the incidence of delivery by Caesarean section, although it rose continuously, increased very rapidly over the age of 35.

Figure 8, also from Baird (1952b), shows the incidence of episiotomy and perineal tears in those women who delivered spontaneously. The incidence of intact perineum fell steadily from 55 per cent in women under 20 to less than 20 per cent in the age group 30–34. The routine management of labour was conservative, in that episiotomy was performed only when it seemed clear that tearing would occur or where progress was delayed by rigidity of the perineum. Bearing in mind that only 60 per cent of primiparae aged 30–34 delivered spontaneously it can be seen that completely "normal" labour, defined as spontaneous delivery within 24 hours with an intact perineum, occurs in only 12 per cent of this age group.

Stewart and Bernard (1954) found that the increase in difficult labour with increasing age in primiparae was attributable to both uterine dysfunction and mechanical difficulty, that is, not only to faulty uterine action or poor expulsive efforts but also to cephalo-pelvic disproportion.

The incidence of fibromyomata of the uterus rises with increasing age, especially in nulliparae. It seems not unlikely, therefore, that there are less obvious changes in the muscle fibres and blood vessels of the uterus which adversely affect its normal function. This might be regarded as analogous to disuse atrophy, and it is not surprising that badly co-ordinated and weak uterine contractions in labour should increase with age. Again, there is reason to believe that the rigidity of the pelvic joints and ligaments and the resistance of the soft tissues of the pelvic floor increase with age in the absence of childbearing, so that even in the absence of cephalo-pelvic disproportion the uterus of the elderly primigravida has to overcome a greater resistance than that of the young primigravida (Turnbull, 1957). This may explain why, in Stewart and Bernard's series, difficulty attributed both to uterine dysfunction and mechanical resistance increased as maternal age rose in primiparae. The picture is, of course, altered in multiparae where the joints, ligaments

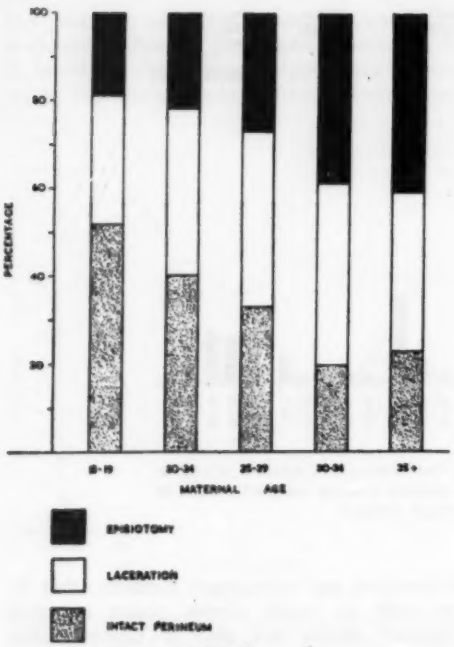

FIG. 8

The incidence of episiotomy and perineal laceration at spontaneous delivery in relation to maternal age at first delivery in a series of Aberdeen primiparae in the years 1949 and 1950. (From Baird, 1952b.)

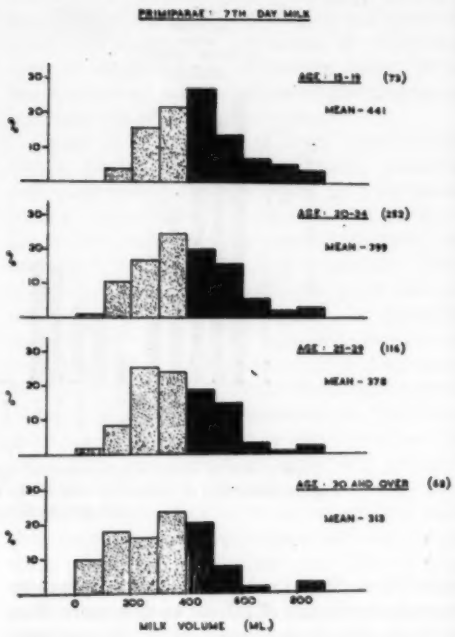

FIG. 9

The distribution of 7th day milk yield in relation to age in primiparae. The arbitrary division into black and stippled areas at 400 ml. was made to accentuate the difference between age groups.

and soft tissues have previously been stretched; the uterus therefore has less resistance to overcome so that uterine dysfunction is relatively rare and age is of much less consequence than in primiparae.

Lactation. It is important that "lactation" should be clearly distinguished from "breast feeding". Lactation refers to the production of milk, a process which is initiated automatically and involuntarily after delivery. Breast feeding, although it obviously implies a maintenance of lactation, depends also on a wide variety of factors from physical health to attitudes and customs.

Figures 9 and 10 show the relationship of the yield and fat content of milk to maternal age in 509 primiparae. Both show a progressive and marked deterioration as age increases, and the fall is obvious even between the 16–19 and the 20–24 age groups. In view of these findings it is not surprising that the number of mothers who succeed in initiating breast feeding becomes progressively less as maternal age increases. This has been shown in 2,461 primiparae delivered in Aberdeen Maternity Hospital between 1951 and 1953 (Hytten, 1954a). The incidence of breast feeding at discharge from hospital, usually between the 8th and 10th days, falls progressively from 88·5 per cent in primiparae of 16–19 to 50 per cent in women of 35 or over.

This falling incidence is very largely due to poor lactation, that is, to an inability to produce sufficient milk of good quality to provide adequate nourishment for the baby (Hytten, 1954a). The incidence of other causes of failure

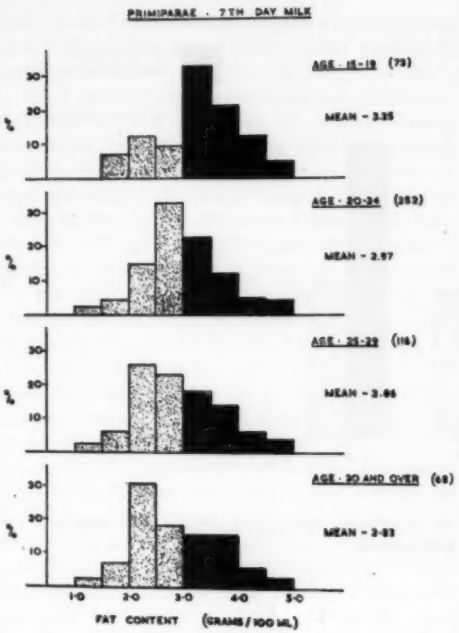

FIG. 10

The distribution of fat content of 7th day milk in relation to age in primiparae. The arbitrary division into black and stippled areas at 3·0 grams/100 ml. was made to accentuate the difference between age groups.

of breast feeding in hospital, such as difficulty with breasts and nipples, a sick baby, or maternal disease, is influenced very little by maternal age.

The yield of milk depends upon the amount of glandular tissue in the breasts, which Hytten (1954b) estimated by measuring the difference in size of the breast between early pregnancy and the start of lactation, since it is likely that growth during pregnancy is largely confined to glandular and duct tissue. In 77 primigravidae the correlation coefficient of breast enlargement and 7th day milk volume was 0·46, but increased to 0·53 when the influence of age was eliminated. The difference, though small and not statistically significant, may indicate that for a given breast enlargement the younger primipara produces more milk than the older primipara; she may be in fact more physiologically efficient.

The mean increase of breast size between early pregnancy and the beginning of lactation fell from 258 ml. in those under 20 years of age to 131 ml. in those of 30 years or more. The correlation coefficient relating age to degree of breast enlargement was $-0{\cdot}25$ ($P < {\cdot}01$).

The phenomenon of differing breast reactions to pregnancy with age is clinically obvious. The young primigravida of 18 is usually aware as early as the 2nd or 3rd month of pregnancy of the rapid enlargement of her breasts, which may become tense and slightly tender. The primigravida of 30 is often unaware of any breast change.

We can only speculate on the changes that may occur in breasts which do not function for many years after puberty, but it is tempting to attribute the reduced yield of milk in elderly primiparae to a disuse atrophy of the glandular tissue. Apparently, the changes in the breast which are said to occur during the menstrual cycle are not sufficient to prevent this "atrophic" effect of increasing age.

The reason for the deterioration in fat content of the milk with increasing age is equally obscure but it is perhaps not unreasonable to assume that the reduced proliferation of glandular tissue in response to pregnancy is associated with reduction of efficiency of the glands themselves.

Breast Feeding. It has been shown above that the proportion of women breast feeding at the time of leaving hospital (about a week after delivery) falls with increasing age.

In the Aberdeen Maternity Hospital it is tacitly assumed that all women will attempt to breast feed. The baby is put to the breast routinely unless there are definite medical contraindications or unless the mother has firmly stated her intention to bottle feed. Much care is taken and time spent in encouraging the mother in the lying-in wards; most patients believe that "they make you breast feed in hospital".

Breast feeding in hospital should be relatively easy; the mother has no domestic worries and little to do except feed her baby; the baby itself is usually sleepy in the warmth of the hospital and its requirements during its first few days of life are minimal. Since in addition the patient feels that she is expected to breast

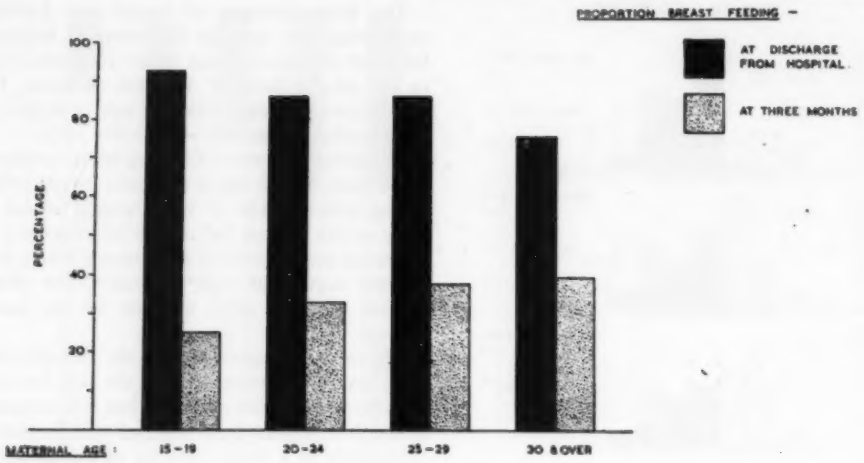

FIG. 11

The relationship between age in primiparae and the incidence of breast feeding at discharge from hospital and at 3 months post-partum.

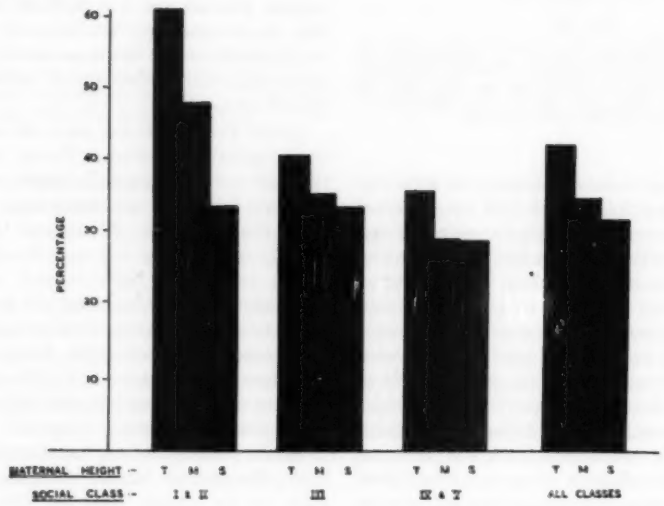

FIG. 12

The relationship of height in primiparae to the incidence of breast feeding at 3 months, in 3 social groups. (Tall=5 feet 4 inches or more, small=under 5 feet 1 inch.)

feed the rate of breast feeding in hospital should reflect closely the actual ability of the mother to produce sufficient milk for the baby's needs.

After the women leave hospital the characteristic fall in the incidence of breast feeding associated with increasing age begins to change and, by the second month, the age gradient is reversed so that the breast feeding rate *improves* with increasing age. By three months the contrast is striking; less than 25 per cent of women under 20, but about 40 per cent of women over 30 are still breast feeding (Fig. 11). At six months, the incidence of breast feeding in these two groups is 14 and 31 per cent respectively.

It was pointed out in the first part of this paper that differences of age in primigravidae imply a whole range of other differences, ranging from social class to height and general health. Figure 12 shows the association of height and social class with the incidence of breast feeding at three months. Height exerts its effect within each social class and the influence of social class is evident in women of comparable height. These findings are consistent with the belief that both physique and social circumstances at the time of breast feeding affect its incidence. The sequence of cause and effect is complex, but although the relative influence of each of the many factors involved is not easy to determine separately, the overall picture is fairly simple.

Breast feeding, once established, is most likely to be successfully maintained by healthy women, who are able to obtain sufficient food and have a good enough appetite to eat it, who can take the responsibilities of caring for a baby in their stride and who believe that breast feeding is best. Experience suggests that such features are most common in the older primigravidae. They are better grown, healthier and better educated and eat a better diet than the very young primigravidae; they more often express the intention to breast feed and do in fact carry out their intention when possible (Baird and Scott, 1953).

Conversely, the younger women are more often in poor health and more often live in a poor environment. The quality of their diet is in some respects inferior (Thomson, unpublished). They are often less determined to breast feed and more easily swayed by advice from neighbours and relatives to change over to bottle feeding. Their chances of breast feeding are impaired by a great many adverse circumstances which often act together. In this way, the physical benefits of youth which permit a high incidence of good lactation are more than countered in a very short space of time by the bad effects of impaired health and poor environment which are common in young primigravidae.

Summary and Conclusions

Voluntary postponement of the first pregnancy after the age at which physical maturity is attained increases the risk of sterility and the chances of difficulty in labour, as well as those of stillbirth. Ability to lactate satisfactorily is also diminished. In biological terms, it would seem reasonable to conclude that the ideal age for a woman to start childbearing is soon after physical maturity is attained, say about ages 18 to 20. Before 18, maternal growth may compete with foetal growth.

Man is a social as well as a biological animal. Social maturation is rarely complete and an economically advantageous and secure position in society is not attained until the middle twenties at least. McKeown (1954) has concluded that the best time for a woman to have a first baby is between the ages of 25 and 30. The infant mortality is then low, because the children born are well cared for; there is therefore least wastage of infant life and reproductive effort. But it should not be inferred that a woman from the slums, of the type who usually has her first baby before the age of 20, would produce a stronger and healthier baby if she postponed the process for five to ten years. The fact is that the type of woman who starts childbearing between the ages of 25 and 30 usually has the advantages of a good education and relatively high social standards and yet is not old enough to have incurred a serious decline of physiological efficiency.

In the complex society in which we live, there may be very good reasons why women should not start childbearing too early. The biological advantage of physiologically efficient reproduction may be less important than the social advantages of adequate knowledge and experience, and of high aims for the children.

Leaving aside the question of primary infertility, the primigravida aged 30 is much more likely than one aged 20 to have a difficult labour and the baby to be stillborn, unless the pregnancy and labour are very carefully supervised. For the baby of the elderly primipara, pre-eclampsia, postmaturity and long labour are particular dangers, but these immediate dangers can be largely obviated by the avoidance of undue prolongation of the pregnancy, and the frequent use of Caesarean section (Baird, 1955; Turnbull and Baird, 1957).

The decline of breast feeding may be regrettable, but the popularity and efficacy of modern artificial feeding are such that ability to lactate, a function which deteriorates steadily with age in primiparae, does not impair the baby's chance of survival or of satisfactory growth.

It has been suggested that the increasing rigidity of the pelvic soft tissues, leading to rising rates of prolonged and difficult labour and of episiotomy and perineal tear, and the decreasing ability of the breasts to secrete milk with increasing maternal age may represent a form of tissue degeneration akin to disuse atrophy. This, of course, is speculation. Future research should be directed to determining the essential physical and biochemical nature of the change in ageing tissues, especially those which do not function but do undergo cyclical development and regression. The clinical data point clearly to the existence of such a change, but little fundamental research seems to have been done on the subject. A knowledge of the mechanisms involved might make it possible to preserve youthfulness and to postpone deterioration. Clinical observation indicates that impaired growth and inferior health are associated with the earlier appearance of the signs of ageing. Ageing may, in the last analysis, be a question of cellular nutrition. Tissues in a fully adequate culture medium do not, apparently deteriorate with age; and what is possible in a test tube might eventually be possible *in vivo*.

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PLASMA AND BLOOD VOLUME CHANGES IN LATE AND PROLONGED PREGNANCY

BY

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"STUDIES of blood volume give a new outlook on many problems which long were considered settled. These researches illustrate again the dictum of Francis Bacon in 1606 when, in his *Novum Organum*, he inveighed against authority in learning and pointed out that in science nothing can ever be considered settled because while the facts may remain the same, the viewpoint is changing constantly. The pure science of today is the applied science of tomorrow" (W. J. Mayo, 1929).

The changes in the blood volume in pregnancy have been of interest to investigators since the earliest experimental work of Welcker in 1854. Using various methods in both animals and humans, the general picture of an increased plasma and blood volume towards the end of pregnancy has been established. The changes which occur in the last few weeks of pregnancy are, however, not settled because of somewhat conflicting results obtained by various observers. These conflicting results were obtained firstly because of the natural variations in individual women, secondly because of technical difficulties associated with the method used and thirdly because of the long time intervals between estimations. All series reported, where repeated estimations have been made on the same patient have, of necessity, been on small numbers of patients because of the difficulties involved in accurate estimations of blood volume.

Thomson *et al.* (1938) reported a progressive increase in the blood volume, reaching a maximum during the ninth lunar month and decreasing during the tenth lunar month. However, this decrease was not observed in all cases. Roscoe and Donaldson (1946), McLennan and Corey (1950) and White (1950) could not confirm any significant pre-labour decrease in plasma or blood volume.

Other workers, Caton *et al.* (1949, 1951), Kjellberg *et al.* (1950) and Gemzell *et al.* (1954) found that a slight insignificant decrease occurred during the four weeks before delivery.

Although some of the pregnancies studied in these reports might be considered prolonged all observations have been computed in relation to the date of delivery. Only Thomson *et al.* (1938) and Gemzell *et al.* (1954) note the duration of pregnancy in the individual cases and these authors record no differences between those pregnancies which terminate prematurely and those which terminate after term.

The object of this further study of the plasma and blood volume in late pregnancy was to determine if there was a statistically significant decrease in the plasma volume in late pregnancy, to determine if this decrease had any relationship to prolonged pregnancy and to observe any differences in the group with prolonged pregnancies when compared with those who delivered near the expected date and those who delivered prematurely.

METHOD

Selection of Cases

Fifty patients who agreed to co-operate were selected for study. In all cases, the patient's menstrual history, the date of the last menstrual period and other relevant data were examined to confirm the duration of pregnancy before any blood volume estimations were carried out. When the study was commenced, patients were

selected at 36 weeks and estimations made at 2- to 3-weekly intervals and if possible when the patient was admitted in labour. Three patients were studied from early in their pregnancies and followed through to confirm the previously reported findings. Later in the study when it was found that the pattern in late pregnancy was not completely determined by these estimations, further patients were studied from 28 weeks until delivery.

Thirty-eight of the 50 patients were normal throughout their pregnancies. Six patients manifested signs of hypertension, 6 patients developed pre-eclampsia in late pregnancy and one patient was anaemic. Surgical induction of labour was carried out in 5 cases.

Method of Plasma Volume Estimation

The method used was an Evans Blue dye technique. This method was chosen as it had been shown to be reliable, a considerable amount was known of the fate and distribution in the body of Evans Blue (Rawson, 1943; Noble and Gregersen, 1946; Barnes, Loutit and Reeve, 1948; Steinbeck, 1950) and it had been shown that it does not cross the placenta or enter the liquor (Gibson and Evans, 1937). Furthermore, it presented certain advantages in that tests could be carried out by the author without dependence on technical assistance and the method used at any time of the day or night. This was essential as a number of the estimations were to be carried out in labour.

The extraction technique based on that described by Bedwell, Patterson and Swale (1955) was used as consistent extractions of 97 per cent were obtained and difficulties with lipaemia and haemolysis were eliminated. The subjects did not need to restrict their meals and, apart from an initial rest before the test was carried out and the actual injection, suffered no inconvenience.

Technique

Special containers were prepared containing two 20 ml. syringes and one specially calibrated 10 ml. syringe autoclaved and ready for use. With special marking on the 10 ml. syringe, the exact volume was obtained consistently and by using four specially calibrated syringes only for the whole series of estimations, by measuring the volume in the same way on each occasion and by using the same method of delivery, the amount of dye delivered to the patient was kept constant. Luer fittings were used throughout. All the tests and extractions were carried out by the author to keep any errors in technique consistently to a minimum.

The *reagents* used were those recommended by Bedwell *et al.* (1955). The Evans Blue dye (B.D.H.) was prepared in two batches for the tests. The same Evans Blue powder was used for all tests but owing to a number of breakages of the glass ampoules during autoclaving and storing, a second batch was made during the later part of the tests. The dye was made up to contain about 15 mg. in 10 ml. The second batch was standardized against the first batch using an Agla microsyringe. Nevertheless, in no instance were tests carried out with the one patient using the two different batches of dye. During the time of storage in a refrigerator (18 months), there was no deterioration in the dye as shown by deposition or optical density change.

The *apparatus* (Fig. 1) was made in the workshops at Hammersmith Hospital, London, so that more than one extraction could be carried out at a time.

The filter is a modification of that recommended by Bedwell *et al.* Four filters were set up in parallel against a white background. They were surrounded by a water jacket of glass so that the progress of the extraction process could be visualized while the water heated in the reservoir was circulating around the system of filters. The dimensions of the inner tube of the filter were 2 cm. in diameter and 10 cm. in length, in its wide upper portion below which it tapered to form the neck of the filter. The circulating water maintained a temperature of 40° C. in the column and the water bath for the reagents was kept at 55° C. Satisfactory extractions were obtained using these temperatures.

Method of Injection of Dye and Collection of Samples

A venous sample of blood was obtained from an antecubital vein without stasis. Ten ml. of

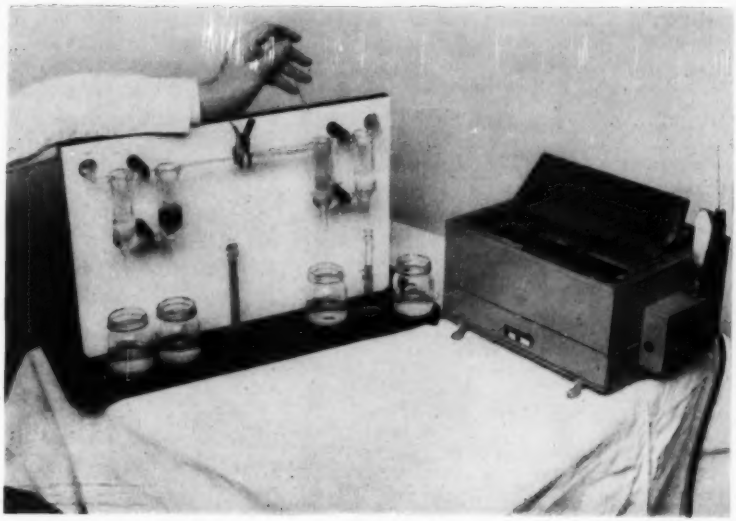

FIG. 1

Evans Blue dye was injected through the same needle over a period of about one minute. When the plunger reached the bottom of the syringe, 4–5 ml. of blood was withdrawn and re-injected. This was repeated and the needle withdrawn. This technique was used in all cases.

Ten minutes later, a further venous sample was obtained from the opposite arm without stasis.

Four ml. of the initial sample was placed in a bottle containing a small quantity of Heller and Paul oxalate anticoagulant mixture. This was used to determine the packed cell volume. If previous estimations had been carried out, a further sample of 8 ml. of blood was placed in a bottle which contained 0·2 ml. of dried heparin. The second venous sample (about 14 ml.) was also placed in heparin bottles. The blood was centrifuged and the plasma removed and stored, until the extraction and estimation of the plasma volume was carried out.

Extraction Technique

In general, two or three extractions were carried out simultaneously. It was found that although it was possible for a single operator to work four columns at once, it was more convenient to operate a smaller number of columns. All additions to the column once formed were run carefully down the side of the funnel. At no time was the column allowed to be free of fluid.

Each estimation was made in duplicate, although on some occasions due to technical difficulties one column was abandoned. Four ml. of plasma was used for each extraction but, if necessary, smaller volumes were used for the second estimation.

A plug of chemical cotton was packed into the neck of the filter sufficiently tightly to allow a flow rate of approximately 1 ml. per minute when using a 10 cm. column of distilled water. Celite suspended in teepol saline (1 in 200) was transferred to the column using a wide-bore Wright's pipette and allowed to settle to form a layer 1–2 cm. deep. When about 1 cm. of fluid remained above the celite, the cellulose-celite suspension was added and washed twice with 10 ml. of teepol saline. This formed the adsorbing layer above the celite.

To 4 ml. of plasma, 2 ml. of 50 per cent teepol was added and after warming the plasma was transferred to the column. The container was washed with teepol saline and this added to the column. The dye was adsorbed to the cellulose and the plasma, together with any haemolyzed blood and fat, was carried through the column. When the eluent was clear, 35 per cent acetone in water was added and the dye moved as a sharp band down the column. The filter tip was washed with distilled water before the dye reached the lower part of the column and when it was in the lower part of the column, the eluate was collected in a 10 ml. graduated cylinder. The dye was collected and when the eluate was cooled, it was made up to 10 ml. with 35 per cent acetone.

Measurement

A standard was prepared in duplicate using an "Agla" microsyringe (as recommended by Barnes *et al.*, 1948). For this, 0·03 ml. of Evans Blue from the same ampoule that had been used for the test was placed in a 10 ml. graduated cylinder and made up to 10 ml. with 35 per cent acetone.

The optical density of the tests and the standards were read against 35 per cent acetone in a Unican S.P.500 spectrophotometer. The readings were made with the tungsten light source, using a wave length of 624μ. When previous tests had been made, the optical density of the post-test sample was compared with that of the pre-test sample while the optical density of the standard was compared with that of 35 per cent acetone.

Packed Cell Volume

The packed cell volume measured was that of the red cell mass and did not include the "buffy" layer. The method of centrifuging used was that advised by Mollison (1956) and correction was made in the calculation for the trapped plasma (Chaplin and Mollison, 1952).

Calculations

The estimation of the plasma volume was made from a comparison of the optical densities of the tests and the standards. A correction of 3 per cent was made for dye retained in the

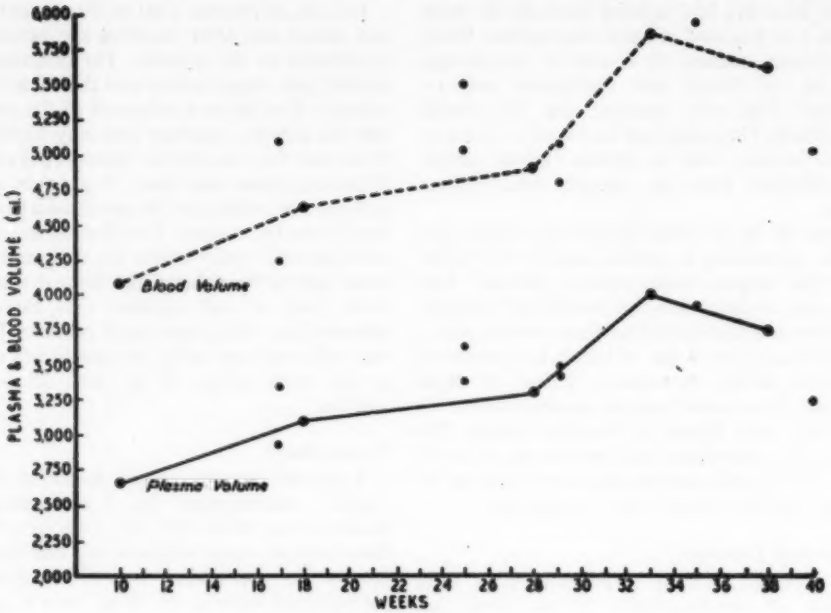

FIG. 2

General picture of plasma volume and blood volume in pregnancy.

TABLE I

Plasma Volume, Packed Cell Volume and Total Blood Volume in Cases Studied from Early Pregnancy

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 4—276 days:						
10	50·8	2,650	52·124	1,743	35·1	4,080
18	52·6	3,115	59·153	2,023	32·8	4,635
28	56·4	3,280	58·197	2,076	32·8	4,880
33	57·1	3,950	69·172	2,500	32·3	5,835
38	57·4	3,745	65·243	2,370	33·3	5,615
Case 5—281 days:						
17	67·7	2,795	41·266	1,579	33·8	4,220
25	68·2	3,375	49·501	1,896	32·8	5,020
29	67·5	3,415	50·593	1,947	32·8	5,060
35	67·7	3,910	57·729	2,209	33·8	5,905
Case 7—282 days:						
17	65·0	3,330	51·230	2,018	35·7	5,180
25	72·5	3,610	49·793	2,111	34·3	5,485
29	74·5	3,470	46·608	1,983	28·4	4,780
40	78·6	3,245	41·311	1,823	35·2	5,010

column. This correction was determined after a series of 6 tests had been carried out and the range of extraction was found to be 96·2 to 97·8 per cent of the amount of dye put into the column.

For the calculation of the total blood volume, a constant ratio of total/peripheral packed cell volume of 0·91 was used. This figure, recommended by Mollison (1956) has been used in all Tables. Caton *et al.* (1951) consider that this ratio varies with the duration of pregnancy and the changes in total blood volume using the constant ratio of 0·91 and the changing ratio of Caton *et al.* are shown in Figure 4.

Results

General Pregnancy Changes

Three cases were studied from early pregnancy (Fig. 2). Case 4 showed a relative rise in the plasma volume of 17 per cent from the 10th to the 18th week, of 24 per cent by the 28th week and of 49 per cent by the 33rd week and then a fall to 41 per cent 6 days before delivery. The total blood volume showed similar changes. (Table I.)

Plasma Volume Changes in Late Normal Pregnancy

Patients Delivered During the Period 262–273 Days

In 4 of the 7 cases in this group, multiple estimations were carried out and in all cases there was a decrease in the plasma volume during the 4 weeks before delivery. (Table II.)

Patients Delivered During the Period 274–279 Days

Of the 12 patients in this group, multiple estimations were carried out in 8. Five were normal, 2 hypertensive and 1 pre-eclamptic. The 5 normal patients did not show a completely consistent pattern. Cases 4, 23 and 27 showed a drop in plasma volume before the onset of labour, while Cases 38 and 41 showed a slight rise. Case 41 had some oedema of the hands and feet and, although pre-eclampsia was suspected to be the cause of this increase in plasma volume, no other manifestations were found. The results of these cases are presented in Table III. (For Case 4, see Table I.)

Table II

Plasma Volume, Packed Cell Volume and Total Blood Volume in Women Delivered During the 38th Week (Cases 17, 21, 28, 35)

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 17:						
33	59·5	3,125	52·521	1,894	31·8	4,580
37	61·3	2,770	45·187	1,659	31·8	4,060
5 days post-partum	54·5	2,750	50·458	1,736	38·0	4,435
Case 21:						
32	72·3	3,475	48·077	1,931	36·7	5,490
36	74·9	3,090	41·255	1,688	37·7	4,960
Case 28:						
35	52·5	3,210	61·142	2,098	40·3	5,380
37	53·5	2,790	52·149	1,812	40·3	4,670
Case 35:						
36	59·9	2,930	48·915	1,854	29·9	4,180
38	59·9	2,900	48·414	1,835	34·7	4,440
In labour						

TABLE III

Plasma Volume, Packed Cell Volume and Total Blood Volume in Women Delivered During the 39th Week (Cases 4, 23, 27, 38, 41)

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 23:						
32	70·8	3,930	55·508	2,312	34·2	5,975
36	74·2	3,705	49·932	2,129	35·7	5,760
38	75·0	3,575	47·667	2,043	35·7	5,560
Case 27:						
36	64·2	3,280	51·090	2,000	34·6	5,015
39 (274)	66·2	3,510	53·021	2,102	35·1	5,410
39 (276) .. .. In labour	65·0	3,180	48·923	1,916	38·8	5,195
Case 38:						
35	63·6	3,080	48·428	1,893	33·7	4,655
38	65·0	3,165	48·692	1,918	35·6	4,915
Case 41:						
36	64·1	2,670	41·654	1,571	32·8	3,975
38	63·6	2,770	43·616	1,748	33·8	4,185

Patients Delivered During the Period 280–286 Days

There were 15 patients in this group. Multiple estimations were carried out in 13 and, of these, 9 were normal, 3 hypertensive and 3 pre-eclamptic.

With the exception of Case 25, there were consistent falls in the plasma volume from the 30th week of pregnancy. This became more marked about 10–14 days before delivery. In Case 25, the patient had three tests in a period of 24 days. The patient was blue after the third test and it may be that this final test was fallacious in that there was insufficient protein available for the dye to conjugate with and some dye was taken up directly by the reticulo-endothelial system, thereby giving an apparent increase in the blood volume at this time. The results of these normal cases are presented in Table IV. (For Case 5, see Table I.)

Patients Delivered During the Period 287–293 Days

There were 11 patients who delivered during this period. The seven normal cases all showed a fall in the plasma volume before delivery. The results are presented in Table V.

Patients Delivered On or After the 294th Day

There were 5 patients who delivered between the 294th and 299th days. In 3 normal cases, where multiple estimations were carried out, there was an increase in the plasma volume until between the 36th and 39th weeks. There was then a fall before the onset of labour. (Table VI.)

The changes in the plasma volume can be related to the time of delivery rather than the duration of pregnancy. All cases were grouped in relation to delivery and the average plasma and total blood volume changes are presented

TABLE IV

Plasma Volume, Packed Cell Volume, and Total Blood Volume in Women Delivered During the 40th Week (Cases 2, 3, 5, 8, 25, 26, 29, 40 and 43)

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 2:						
27	69·9	3,535	50·557	1,975	31·2	5,140
31	72·7	3,910	53·760	2,148	32·3	5,745
38	76·1	3,950	51·905	2,147	33·7	5,960
40	76·3	3,520	46·145	1,913	34·3	5,360
Case 3:						
32	61·3	3,445	54·567	2,167	33·7	5,195
34	61·0	3,045	49·918	1,915	35·0	4,685
38	61·3	2,790	46·551	1,755	38·5	4,535
39	61·5	2,770	45·040	1,742	37·5	4,430
40 .. .. .. In labour	60·6	2,600	42·904	1,635	40·8	4,390
Case 8:						
30	65·4	3,960	60·550	2,386	32·3	5,850
33	66·8	4,060	60·751	2,446	29·8	5,650
36	68·5	4,610	67·299	2,744	32·8	6,860
39	67·5	3,930	58·222	2,353	31·8	5,760
Case 25:						
36	73·3	3,385	46·180	1,902	38·4	5,495
38	75·2	3,365	44·747	1,845	40·3	5,635
40	73·4	3,630	49·455	2,039	39·3	5,980
Case 26:						
35	61·8	2,700	43·689	1,646	36·1	4,225
38	63·6	2,620	41·065	1,578	35·6	4,070
40 .. .. .. In labour	64·6	2,605	40·214	1,698	39·8	4,325
Case 29:						
34	59·9	3,010	50·250	1,955	37·7	4,830
38	61·0	2,810	46·065	1,813	34·2	4,270
Case 40:						
36	86·0	4,240	49·302	2,369	29·8	6,040
38	86·0	4,240	49·302	2,369	31·8	6,215
Case 43:						
36	57·2	2,860	50·000	1,810	31·8	4,195
39	58·4	2,700	46·233	1,698	33·8	4,080

TABLE V

Plasma Volume, Packed Cell Volume and Total Blood Volume in Women Delivered During the 41st Week (Cases 10, 16, 19, 24, 31, 33 and 44)

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 10:						
31	58·1	3,445	59·294	2,266	30·8	4,980
35	58·7	3,425	58·345	2,253	32·8	5,095
39	60·9	3,395	55·747	2,190	33·3	5,090
40	62·9	3,170	50·397	2,006	34·2	4,820
Case 16:						
36	58·8	2,700	45·918	1,667	32·8	4,020
39	60·8	2,795	45·970	1,715	36·1	4,375
41 .. .. .. In labour	58·6	2,600	44·368	1,605	35·7	4,045
Case 19:						
36	66·4	3,280	49·397	1,988	36·5	5,165
39	67·5	3,500	51·851	2,108	35·7	5,445
41 .. .. .. In labour	67·9	3,270	48·159	1,970	38·0	5,275
Case 24:						
36	51·3	2,800	54·580	1,931	36·1	4,380
39	50·7	2,815	55·522	1,941	34·7	4,310
41 .. .. .. In labour	50·4	2,465	48·908	1,700	38·8	4,030
Case 31:						
36	63·6	2,830	44·496	1,726	31·8	4,150
39	64·6	2,810	43·498	1,703	34·7	4,305
Case 33:						
36	67·3	4,340	64·487	2,452	27·8	6,010
41	69·5	3,830	55·107	2,140	31·2	5,565
Case 44:						
36	71·4	3,580	50·140	2,093	37·7	5,745
39	70·9	3,445	48·589	2,026	39·3	5,675

TABLE VI

Plasma Volume, Packed Cell Volume and Total Blood Volume in Women Delivered On or After the 294th Day (Cases 1, 6 and 32)

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 1:						
36	64·0	3,210	50·148	1,922	37·3	5,110
39	65·4	3,805	51·198	2,251	39·9	6,330
41	66·3	3,350	50·535	1,971	41·3	5,710
42	65·4	3,325	50·856	1,967	40·4	5,580
In labour						
6 days post-partum	59·0	3,345	56·685	2,065	41·7	5,740
Case 6:						
35	51·0	2,650	51·960	1,790	38·9	4,340
38	52·4	3,330	63·549	2,235	34·7	5,100
40	52·5	3,055	58·190	2,036	35·5	4,740
42	52·5	2,980	56·761	1,987	36·5	4,690
In labour						
Case 32:						
34	77·2	3,755	48·639	2,052	33·7	5,665
37	81·7	3,980	48·718	2,128	34·7	6,095

in Figures 3 and 4. There is a fall in the plasma volume during the period 8 weeks before delivery and this is most marked in the 2 weeks before delivery. The fall in the 2 weeks before delivery is statistically significant ($t=3·4485$, $p<0·01$).

PLASMA VOLUME IN PREGNANCIES WHICH TERMINATE PREMATURELY, AT THE EXPECTED TIME AND BEYOND THE EXPECTED DATE

If the cases of normal pregnancy and those with hypertension (these have a picture similar to the normal group—see below) are grouped, based on the date of delivery, and, if the plasma volume estimations at any particular time are compared, it will be found that, as the duration of pregnancy increases, the plasma volume increases (Fig. 5). Thus, if the plasma volume in the 2 weeks before delivery is studied, the plasma volume of the 37–38 weeks delivery group averages 2,890 ml., the plasma volume of the 39 week delivery group averages 2,945 ml., the plasma volume of the 40 week delivery group averages 3,055 ml. and the plasma volume of the 41–43 weeks group averages 3,165 ml.

There would therefore appear to be a larger circulating plasma volume in the patients whose pregnancies are prolonged than those whose pregnancies are of average duration. The average plasma volume of patients delivered prematurely is smaller again. Despite these differences, however, the pattern of plasma volume changes in late pregnancy is the same whether the pregnancy is prolonged or not.

Plasma Volume in Patients with Hypertension

There were 6 patients who had hypertension without an associated pre-eclampsia. In 3 cases (9, 14 and 37), labour was induced. The general pattern of plasma volume changes in these cases is similar to the normal pattern and presumably the rise in blood pressure necessitating the induction of labour had followed the normal fall

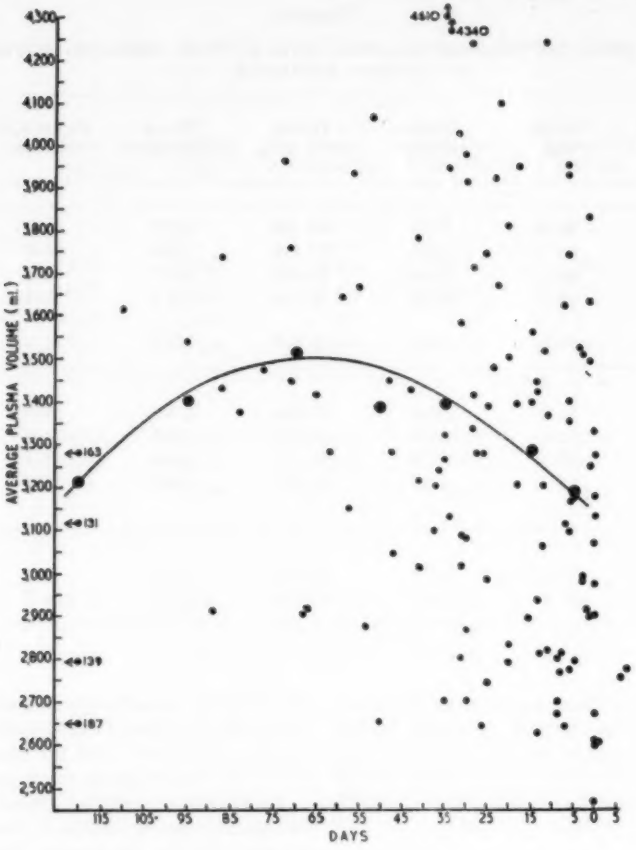

FIG. 3

Total plasma volume related to date of delivery.

in the plasma volume at this time (Fig. 6). The results are presented in Table VII.

Plasma Volume in Patients with Pre-eclampsia

There were 6 patients who had pre-eclampsia, in some cases associated with hypertension. Labour was induced in 2 cases (12 and 20). The results are presented in Table VIII and the general pattern in Figure 7. It would appear that in these cases, none of which could be considered severe, there was little fall in the plasma volume in late pregnancy.

Plasma Volume with Foetal Distress

There were 6 cases (2, 10, 11, 13, 14 and 50—see Tables I–VIII) where foetal distress was present. No infants were lost.

The plasma volume changes were normal in

TABLE VII

Plasma Volume, Packed Cell Volume and Total Blood Volume in Women with Hypertension Without Pre-eclampsia (Cases 9, 13, 14, 18, 37 and 42)

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 9:						
32	64·3	3,660	56·920	2,166	35·4	5,640
37	66·2	3,415	51·586	2,009	35·7	5,260
39	65·8	3,415	51·899	2,009	36·2	5,355
41 .. .. .. In labour	67·4	3,065	45·474	1,782	36·7	4,840
Case 13:						
28	68·2	3,425	50·219	2,039	35·2	5,285
32	72·7	3,350	46·080	1,948	35·1	5,160
36	72·7	3,085	42·434	1,794	37·5	4,935
39	73·2	2,990	40·846	1,728	37·5	4,785
Case 14:						
32	73·2	3,145	42·964	1,728	38·1	5,080
35	74·6	3,240	43·431	1,761	36·7	5,120
38	75·8	3,200	42·216	1,730	37·7	5,135
40 .. .. .. In labour	76·0	3,125	41·118	1,689	38·2	5,060
Case 18:						
30	64·1	2,900	45·241	1,813	33·8	4,380
36	67·0	2,740	40·895	1,671	37·1	4,355
39	69·1	2,970	42·981	1,800	39·3	4,890
Case 37:						
36	69·9	2,640	37·768	1,483	35·2	4,075
38	70·8	2,670	37·712	1,483	37·1	4,250
Case 42:						
36	70·7	2,930	41·443	1,646	30·8	4,235
39	73·8	2,910	39·431	1,617	30·8	4,205

TABLE VIII

Plasma Volume, Packed Cell Volume and Total Blood Volume in Patients with Pre-eclampsia (Cases 7, 12, 15, 20, 22 and 34)*

Duration of Pregnancy (weeks)	Weight Kg.	Plasma Volume	Plasma Volume/Kg.	Plasma Volume/Sq.m.	Packed Cell Volume	Blood Volume
Case 12:						
27	69·7	3,735	53·586	2,087	36·2	5,765
31	72·0	3,640	50·590	2,011	34·8	5,580
35	73·5	4,030	54·830	2,202	35·3	6,230
38	76·2	3,950	51·837	2,147	38·9	6,465
Case 15:						
35	56·1	3,010	53·654	1,955	33·2	4,505
37	57·5	3,200	54·700	2,065	30·8	4,625
39	58·8	2,890	49·149	1,841	30·8	4,175
Case 20:						
36	61·3	2,500	40·783	1,592	37·1	3,975
39	63·4	2,640	41·640	1,610	37·1	4,200
40	64·1	2,670	41·653	1,618	36·1	4,180
In labour						
Case 22:						
36	72·3	3,200	44·260	1,788	36·3	5,025
39	71·3	3,560	49·929	2,000	37·6	5,690
41	74·5	3,490	46·877	1,918	37·6	5,590
Case 34:						
36	75·4	3,260	43·236	1,842	39·3	5,370
39	76·3	3,510	46·003	1,972	38·4	5,700

* For Case 7, see Table I.

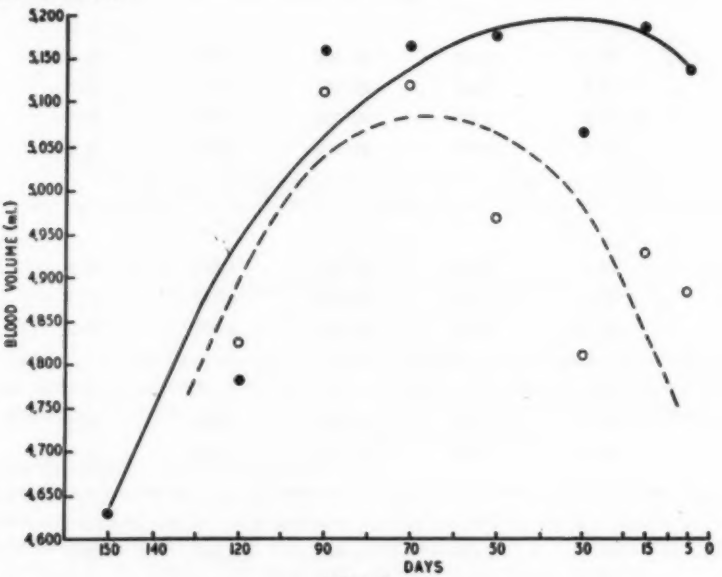

FIG. 4

Total blood volume related to date of delivery.

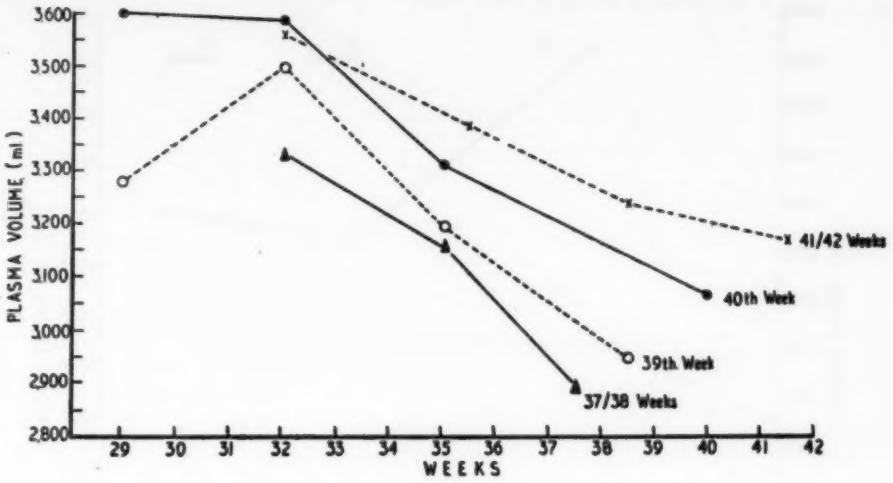

FIG. 5

Total plasma volume in late pregnancy related to duration of pregnancy.

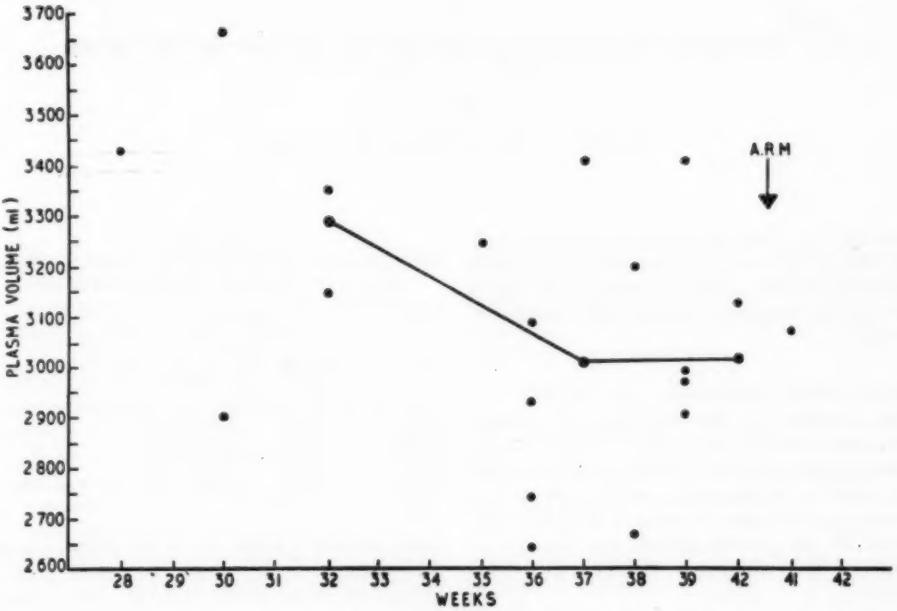

FIG. 6

Hypertension—plasma volume in late pregnancy.

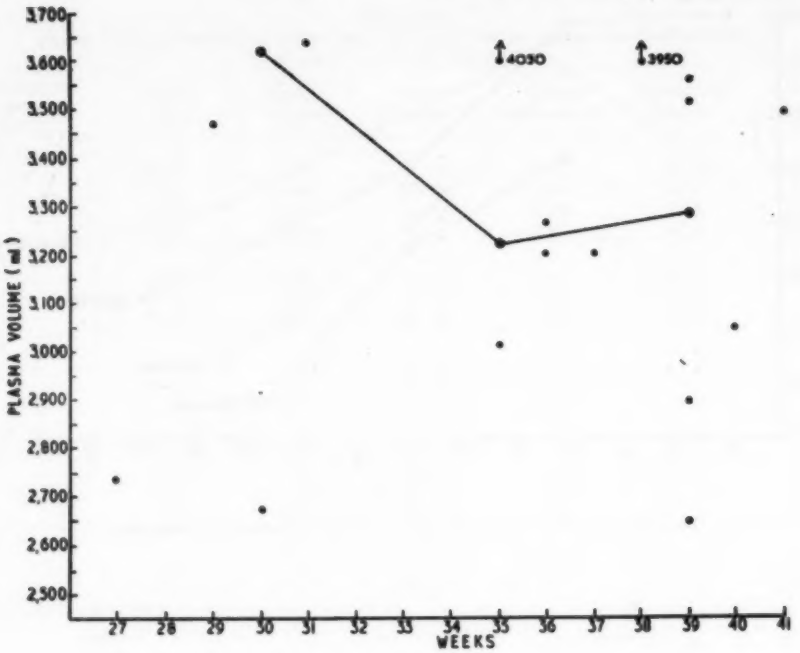

FIG. 7

Pre-eclampsia—plasma volume in late pregnancy.

these cases for the duration of pregnancy (Fig. 8). The foetal distress could be related to other associated factors, such as hypertension, age of the patient, prolonged labour and contracted pelvis.

Plasma Volume Analyzed by Age and Parity

An analysis of the final plasma volume estimations carried out in the 10 days before delivery showed that the average plasma volume was higher in women aged over 25 years than in women aged less than 25 years. This is probably related to the general growth and increase in weight which continues through the third decade.

A similar analysis of the final plasma volume estimations by parity, taking age into consideration, showed a slight rise in the parous group. This was reversed when the same plasma volume/kg. were related to parity. The increase of the plasma volume with parity was considered to be due to increased age and weight.

TABLE IX

Final Estimations of Plasma Volume (0–10 Days Before Delivery) by Age and Correlated with Weight

	Absolute		P.V./Kg.
	Average (ml.)	Range	Average
15–19 ..	3,122	2,670–3,490	47·333
20–24 ..	3,107	2,465–3,830	45·628
25–29 ..	3,490	2,605–3,930	52·856
30–36 ..	3,223	2,600–3,950	48·140

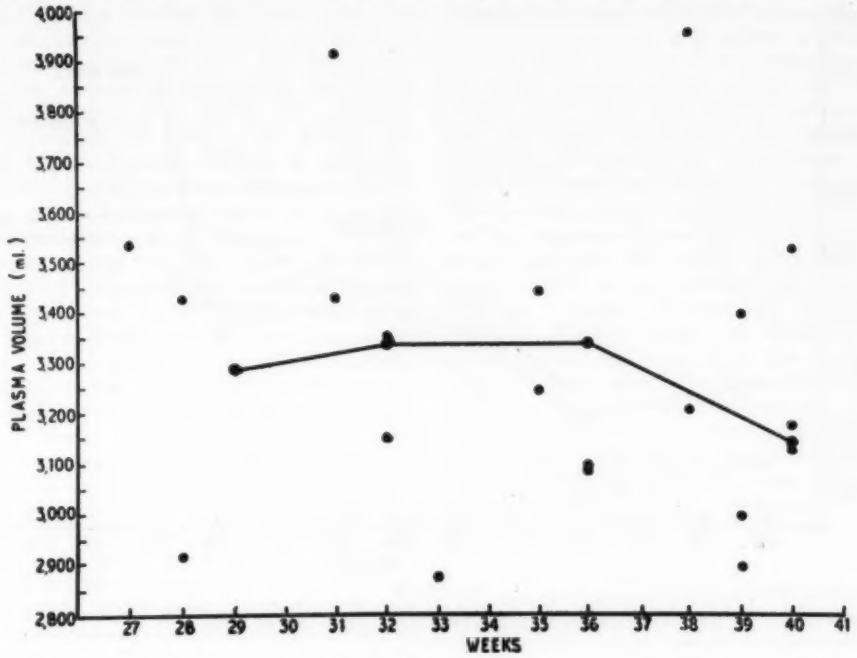

FIG. 8

Foetal distress—plasma volume in late pregnancy.

Plasma Volume Analyzed by Placental Weight and Weight of the Infant

The analysis of the final plasma volume estimations (0–10 days before delivery) in relation to placental weight showed that the average plasma volume was 270 ml. greater in those cases where the placenta weighed more than 22 ounces than in those where the placenta weighed less. The average plasma volume of the 16 cases where the placenta weighed less than 22 ounces was 2,931 ml. while the average plasma volume of the 19 cases where the placenta weighed more than 22 ounces was 3,242 ml.

Analysis of the final plasma volume estimations in relation to the weight of the infant showed that there was a progressive increase in the average plasma volume with the increase in the weight of the infant. This increase in average plasma volume with increase in the weight of the infant would appear to be correlated with placental weight and duration of pregnancy (Table X).

TABLE X

Final Estimations of Plasma Volume (0–10 Days Before Delivery) Correlated with Weight of Infant

Weight	Plasma Volume	
	Average (ml.)	Range
Less than 6½ pounds ..	2,885	2,600–3,395
6½–7½ pounds	3,064	2,670–3,830
7½–8½ pounds	3,212	2,605–3,970
More than 8½ pounds ..	3,366	2,890–3,950

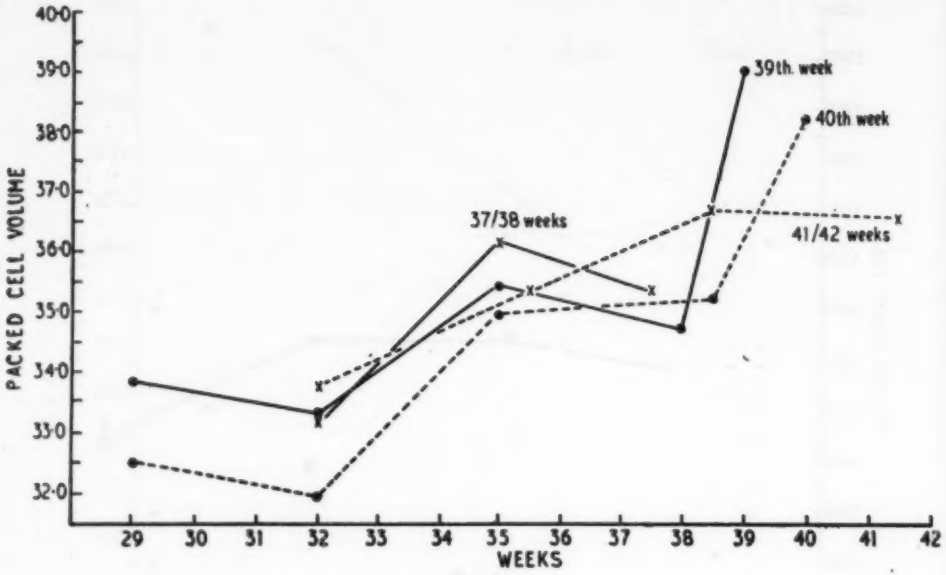

FIG. 9

Peripheral packed cell volume changes—normal cases.

Changes in the Packed Cell Volume and Total Blood Volume in Late Pregnancy

During the last 3 months of pregnancy, the peripheral packed cell volume undergoes changes as the plasma volume decreases. The changes in relation to the apparent gestation time can be seen in Figure 9.

The packed cell volume in the group which delivered between the 280–286 days showed an average increase from 31·2 per cent at 30 weeks to 35·2 per cent at 39 weeks. Similar changes can be seen in the whole series. The increase in the average packed cell volume in the two weeks before delivery and the period 8 to 4 weeks before delivery is statistically significant ($t=5·4$, $p<0·001$ and $t=5·91$, $p<0·001$).

As the packed cell volume increases while the plasma volume decreases, the changes in the total blood volume are not as great as in the plasma volume. Nevertheless, there are changes of a similar nature to the plasma volume changes (Fig. 4).

DISCUSSION

The observed plasma and blood volume changes in these cases show that there is a statistically significant fall in the plasma volume during the last 2 weeks of delivery. This fall in the plasma volume is related to the time of delivery rather than the duration of pregnancy. During the same time, the peripheral packed red cell volume is increasing and over the last 8 weeks of pregnancy there is an increase of the order of 4 per cent. Such a rise in normal women would support the contention of a physiological hydraemia in mid-pregnancy and levels of haemoglobin concentration up to 10 per cent below the normal 14·5 g. per cent should not be considered abnormal between the 18th and 32nd weeks. Of course, during pregnancy the total body haemoglobin is increasing (Kjellberg *et al.*, 1950; Caton *et al.*, 1951; Berlin *et al.*, 1953).

The average plasma volume figures in this series are a little lower than in most other series

where the dye method has been used. The average plasma volume of 3,187 ml. in the 10 days before delivery is about 100–300 ml. less than that observed by Dieckmann and Wegner (1934), Thomson *et al.* (1938), McLennan and Thouin (1948) and Caton *et al.* (1949). This figure is possibly lower because of corrections made for trapped dye in the extraction method.

The plasma volumes of women delivered after the 40th week are larger than those of women delivered during the 40th week. The plasma volumes of women delivered during the 38th and 39th weeks are smaller again. This finding, although not statistically significant, is supported by the work of Raiha and his colleagues (1956, 1957) on the relation of heart volume and total haemoglobin per cent to the duration of pregnancy. They found that the heart volume increased during early and mid-pregnancy and decreased in late pregnancy. Raiha (1956) also found that, when the heart volume and total haemoglobin per cent of the mother were reduced, the prematurity rate was higher and advised that these patients should rest. He considered that, by doing this, the prematurity rate had been reduced. This would suggest that the duration of pregnancy is directly related to the size of the plasma and blood volume. The larger plasma and blood volume in women where pregnancy is prolonged may be related to the woman's constitutional type. Women, who produce more progesterone, which would delay the onset of effective uterine contractions, may be more prone to have larger plasma volumes and prolonged pregnancies.

In the cases with hypertension without pre-eclampsia, the same pattern of changes was observed as in normal pregnancy. This agrees with White's findings. White (1950) and Freis and Kenny (1948) found that the plasma volume was smaller in pre-eclampsia. This was not confirmed in this series and would indicate a rise in the fluid content of both compartments of the extracellular fluid space, rather than a shift from the vascular to the extravascular space.

The fall in the plasma and blood volume in normal late pregnancy is accompanied in many cases by a slight reduction in weight. In late pregnancy there is also a fall in pregnanediol excretion although Coyle, Mitchell and Russell (1957) could not find any definite correlation with the onset of labour. It is possible that the fall in the plasma volume, weight and pregnanediol production are related findings and that the changes are all due to the diminished formation of steroids by the placenta. An equally acceptable and tempting theory of the blood volume changes is that the placental bed is being reduced and the blood diverted to more normal channels. The concept of the arteriovenous shunt at the placental site and the circulatory changes accompanying it, as proposed by Burwell (1938) and supported by Bickers (1942) and others, have been accepted. Holman (1940) points out that when such a shunt is closed, the associated changes in the circulation also return to normal. This fall in the plasma volume and the associated changes in the peripheral packed cell volume reflect the beginning of this placental shutdown.

Summary

A study of the plasma and blood volume in late pregnancy was undertaken in 50 women. Women whose pregnancies were prolonged were found to have average plasma volumes greater than women who delivered at term and these women had average plasma volumes greater than women who delivered at 38–39 weeks. It is suggested that women who produce more progesterone have greater plasma volumes and prolonged pregnancies.

There was a statistically significant fall in the plasma volume in the 2 weeks before delivery.

During the 8 weeks before delivery there was also a statistically significant increase in the peripheral packed red cell volume. This fall in the plasma volume and rise in the packed cell volume in late pregnancy is considered to be further evidence of the diminution in the size of the arteriovenous shunt at the placental site at the end of pregnancy.

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THE ELECTROLYTE COMPOSITION OF THE HUMAN UTERUS IN NORMAL PREGNANCY AND LABOUR AND IN PROLONGED LABOUR

BY

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IN recent years a growing interest has been taken in the ionic composition of the body in various physiological and pathological states. Considerable knowledge has been gained of the total body electrolytes by means of balance studies, and measurements of the serum electrolytes have become an everyday clinical tool. Changes in the electrolyte composition of individual organs in response to physiological and pathological change are not nearly so well understood.

In excitable tissues, some relations between the ionic balance of the cell and its environment, the membrane potential, and the process of excitation have been established. Certain smooth muscles have been shown to lose potassium from the cells and to gain sodium when they are stimulated to contract by the action of drugs (Parrot, Thouvenot and Longuevalle, 1953; Born and Bülbring, 1956; Tobian and Fox, 1956; Macmillan and Vane, 1956). It is believed that the reverse process occurs during relaxation due to drugs. In uterine smooth muscle cells the membrane potential has been shown to fall during stimulation by oxytocin, in a manner suggesting that similar ionic transfers occur (Woodbury and McIntyre, 1954). Less transient changes in ionic composition of the uterus have been observed following the administration of oestrogen or progesterone to animals (Talbot, Lowry and Astwood, 1940; Horvath, 1954). It seems possible that the activity of uterine smooth muscle may be dependent on the ionic content of its cells.

The electrolyte composition of the human uterus was first determined, mainly on autopsy material, by Kochman and Kruger (1926) and by Treite (1938). Further data on the content of individual electrolytes in relatively isolated cases are given by Rossenbeck (1931), Winkler (1936a, b), Manery and Hastings (1939), Parvianen, Soiva and Ehrnrooth (1950), and Nordenstrahl (1952). Only a few observations on the human uterus (Daniel, 1955; Daniel and Boyes, 1957; Cort and Cort, 1957) have been made since simple and reliable methods for the estimation of sodium and potassium have been available. The present study was therefore undertaken with a view to establishing the electrolyte composition of the human uterus during pregnancy, in labour, and in prolonged labour, using small biopsy specimens taken from the edge of incisions in the uterus at operation. The observations were confined to the myometrium and the majority of the specimens came from the lower segment. A preliminary report on a few of the cases has already been made (Nixon and Smyth, 1957).

While this report was in preparation, some observations on the electrolyte composition of the human uterus in pregnancy and long labour

were presented by Cort and Cort (1957) and we have commented on and confirmed certain of their findings (Hawkins and Nixon, 1957a).

Intracellular Electrolytes

The most intriguing possibility which suggested itself to us in this work was to attempt to find changes in the amounts of the individual electrolytes which lie within the smooth muscle cells of the myometrium. Computation of these intracellular levels depends on determination of the extracellular space volume in the tissue. It is possible to deduce from the plasma levels of electrolytes the composition of the extracellular fluid, assuming this to be an ultra-filtrate of plasma. Subtraction of the total extracellular ions from the total ions in the tissue, found by analysis, gives the intracellular ions (Hastings and Eichelberger, 1937). The main difficulty in such an analysis lies in accurate determination of the extracellular space volume. We are investigating other methods of measurement of extracellular space in tissue biopsies, but the best method available to us during the present study was to use the "chloride space". That is, to make the assumption that all the chloride in the tissue is extracellular and to compute the extracellular space volume from the ratio of total tissue chloride to extracellular fluid chloride concentration. This assumption may be inaccurate. In a number of tissues the fact that a small proportion of the chloride is intracellular has been demonstrated (see Manery and Hastings, 1939; Darrow, 1946), and the possibility that small amounts of chloride are collagen bound has also been suggested.

Some further evidence for the view that estimates of extracellular space based on the chloride assumption are unduly large has been obtained from measurements of the volume of distribution of inulin in tissues. It is believed that inulin diffusion is confined to the extracellular compartment and Davson (1951) expressed the view that this substance provides the best available means of measurement of extracellular space. In certain tissues, the inulin space is some 10–20 per cent smaller than the chloride space, and this suggests that 5–10 per cent of the tissue chloride is intracellular or bound. However, as Cort (1955) has pointed out, there are possible sources or error in inulin space determination which could lead to underestimates, and it may yet prove that chloride space provides a better method of measurement. In the myometrium, the actual extent of any possible deviation from the assumption that all the chloride is extracellular is unknown; the experiments of Horvath (1954) suggest that it is small. We have not, therefore, applied any arbitrary correction such as that suggested by Darrow (1946).

Using such methods, the actual amounts of potassium in the cells may be fairly accurately estimated from the analytical data, since roughly 95 per cent of the potassium is intracellular and even wide errors in extracellular space estimation affect the value obtained very little. Similar considerations apply to calcium and magnesium, which are also largely intracellular. On the other hand, the majority of the sodium in the tissue is extracellular, and the measurements of intracellular sodium levels are very sensitive to errors in extracellular space determination. This means that a systematic error in determination of the space would produce a systematic error in intracellular sodium determination, and only specimens taken from the same site in the uterus are strictly comparable. Even then, intracellular sodium levels measured in this way show some variation. For these reasons, the possibility of a systematic under-estimate, as well as variation in the value obtained, must be borne in mind in interpreting observations of intracellular sodium levels. Similar considerations apply to estimates of intracellular water.

In fact, in the present work, biopsies from different parts of the same uterus usually produced values for intracellular sodium which were in agreement, even though the respective extracellular spaces differed. This was good evidence that the use of the uncorrected chloride space was justified and that this measure of extracellular space was adequate for the computation of intracellular levels.

Our data for "extracellular space" and "extracellular water" are more accurately described as "chloride space" and "chloride space water". The values for intracellular electrolytes are

strictly for the residual space in the myometrium after substraction of the chloride space. We have preferred to adhere to the terms extracellular and intracellular space and to describe above the possible sources of error in the assumption that they are the same as chloride and residual space; the former terms are convenient and convey more easily the nature of the tissue compartments whose composition is of interest.

Methods

Muscle biopsies, weighing 1 to 2 g., were taken from the edges of incisions in the uterus at operation under general anaesthesia. At the same time, specimens of heparinized blood were taken by venepuncture for estimation of the plasma electrolytes. Cases known to have received oxytocic drugs before the biopsies were taken have been excluded from the present study, since we have evidence that the action of the drugs alters the electrolyte content of the uterine muscle.

The piece of muscle was placed at once in a dry screw-capped bottle and transferred to the laboratory. A piece of myometrium was then rapidly trimmed from the centre of the specimen. This was divided into five to ten pieces, each 50 to 200 mg. in weight. One piece was preserved for histological study and, where possible, pieces of myometrium were reserved for estimation of calcium, magnesium, fat, blood, and collagen contents. The remaining portions were rapidly weighed on a torsion balance, allowing minimal opportunity for loss of water, placed in weighed Pyrex centrifuge tubes, dried overnight at 105° C., cooled and re-weighed to measure water content. Three ml. of dilute (Nl.) nitric acid were added to each of the tubes, which were then stoppered and left to soak for 7 days. At the end of that time the contents of the tubes were well mixed and centrifuged. Aliquots of the supernatants were used for the estimation of chloride by Volhard titration, slightly modified from Keys (1937), and of sodium and potassium (by flame photometry).

An EEL flame photometer was employed in the latter estimations. Potassium chloride was used for the standard potassium solutions and sodium chloride for the standard sodium solutions. Nitric acid was not present in the standard solutions as it was found that the addition of amounts of this acid equal to those present in the diluted muscle extracts did not influence the readings.

We have found that estimations of chloride, sodium and potassium in these dilute nitric acid extracts (Lowry and Hastings, 1942) is preferable to the older methods (Van Slyke, 1923; Wilson and Ball, 1928; Keys, 1937) of nitric acid digestion with or without preliminary alkaline digestion (Sunderman and Williams, 1933), for these very small specimens of dried uterus, insufficient for grinding and sampling. For the estimation of chloride the dilute nitric acid method gave consistently higher and more reproducible results than the above-mentioned digestions in strong nitric acid. The extraction of chloride by cold dilute nitric acid is 100 per cent under our conditions since prolonged supplementary 50 per cent nitric acid digestions of supernatant or residue failed to increase the yield.

In a similar way we have verified the cold dilute nitric acid method for sodium and potassium. Alternative methods were investigated; ashing the dried tissues in crucibles for 16 hours at 500° C. and dissolving the ash in dilute hydrochloric acid gave 10 per cent lower values for both sodium and potassium. Digestion of the dried tissue in 50 per cent nitric acid (after Creese, D'Silva and Hashish, 1955) gave the same values for potassium as the dilute nitric acid method, but in our hands the yield of sodium was approximately 5 per cent lower.

The period of 7 days soaking in dilute nitric acid appears to be optimal for the type of dried specimen with which we had to deal; 3 days gave slightly low sodium values, while the extraction of all three ions was 100 per cent at 7 days.

Calcium and magnesium were estimated on a single piece of muscle from each specimen. The muscle was ashed for 16 hours at 500° C. and the residue taken up in 2 ml. warm 0·1 N HCl. Calcium was estimated by the method of Kramer and Tisdall (1921), magnesium by that of Simonsen, Westover and Wertman (1947) using the supernatant left after precipitation of calcium for magnesium determination.

The validity of the sodium, potassium, chloride, calcium and magnesium estimations was repeatedly checked by measuring the recovery of small amounts of added salts, and satisfactory results were obtained. The standard solutions employed were all checked against freshly prepared standards at intervals.

Muscle fat was not estimated routinely since in the majority of cases the small size of the specimens available made this impracticable. Where slightly larger specimens were available, ether-soluble and petroleum ether-soluble fat was measured by the method used by Eichelberger and Bibler (1940). As Manery and Hastings (1939) have observed, the electrolyte calculations are not affected by fat corrections of less than 5 per cent. Fat content was always less than this in specimens of myometrium we have examined, ether-soluble fat lying within the range 0·3–4·2 g./kg., an additional 0·1–1·1 g./kg. being extractable with petroleum ether. We have not, therefore, attempted any correction for fat.

The blood content of the specimens was estimated in many cases. The procedures employed were the chemical methods of Wu (see Bing and Baker, 1931) and Lowry and Hastings (1942), the counting of red cells diffusing from coarsely minced tissue shaken by hand or by machine into saline (Mokotoff, Ross and Leiter, 1952) and a histological method which we are developing. Commonly more than one of these techniques were employed as agreement between them was not entirely satisfactory. They showed that blood content was small (generally of the order of 20 ml./kg.), and insufficient to cause error in the computation of intracellular ionic levels.

Histological sections were kindly prepared by Dr. P. E. Hughesdon, of the Department of Morbid Anatomy, University College Hospital Medical School. The sections were used to confirm that the specimens analyzed were in fact myometrium. Further work on these histological preparations is in progress and the results will be reported elsewhere. Studies of collagen content and related observations are being made on the specimens by Dr. R. D. Harkness, of the Department of Physiology, University College, London, and these also will be reported later.

Plasma and red cell electrolytes were estimated by the methods used by Hawkins and Nixon (1957b). The nomograms given by McLean and Hastings (1935) and Willis and Sunderman (1952) were used to compute ionized calcium and magnesium in plasma.

Electrolyte content of the specimens studied is, in general, given in terms of milli-equivalents per 100 g. dry tissue. For each specimen of muscle several estimates of water, sodium, potassium and chloride were made as described above and the results averaged in terms of m.-eq./100 g. dry tissue; single estimates of calcium and magnesium were made for each specimen. In a few cases where two specimens were available from the same site the results were averaged.

Values were also calculated per kg. of wet muscle. Changes in electrolyte content expressed in these terms were in complete agreement with changes expressed per 100 g. dry tissue, though sometimes they did not reach such a high level of statistical significance.

For convenience, the results are given as mean values for each group of cases. The standard deviations quoted represent variation between patients, since errors of estimation, sampling errors and variation between specimens from the same site were trivial compared with the variation between patients. In general, changes demonstrable at the $P = 0{\cdot}05$ level were considered significant.

Intracellular electrolytes were calculated by the method of Hastings and Eichelberger (1937), basing the calculations on the mean electrolyte content for each specimen, and using a Gibbs-Donnan factor of 0·95 to compute the extracellular fluid ions.

Classification of Clinical Material

(1) *Normal uterus.* For obvious reasons it was possible to obtain biopsies of normal uterus in only a small number of cases and it was necessary to group together patients in proliferative and secretory phases of the cycle. Three patients had abdominal sterilization for psychiatric indications; all were in the proliferative phase. One patient had a total hysterectomy for a very large cyst arising from the pelvis, which later proved to be a benign serous cystoma of the broad

ligament, the ovaries and uterus being normal. One patient had tuberculous adnexitis and a congenitally small uterus, there being adequate evidence of normal hormonal status and of menstrual rhythm. Both the two latter patients were in the secretory phase of the cycle.

(2) *Early pregnancy.* Nine patients had abdominal hysterotomies for termination of pregnancy, at 10, 11, 12, 15, 15, 15, 20, 20, and 20 weeks respectively. The indications were psychiatric (5 cases), carcinoma of the breast (2 cases), pulmonary tuberculosis not responding to treatment (1 case), and bronchiectasis with rapid deterioration in one patient who had had a pneumonectomy. There was no indication of any trend from the 11th to the 20th week and the 9 cases were grouped together.

(3) *At term, not in labour.* Eleven patients who were between 38- and 42-weeks pregnant by dates had elective Caesarean section. The indications were disproportion (4), placenta praevia (2), failed induction, overdue by dates (1), ante-partum haemorrhage with foetal distress (1), ovarian cyst obstructing a breech (1), previous rupture of uterus (1), previous multiple myomectomy, breech and overdue by dates (1).

(4) *Premature labour.* Six patients who went into labour before 38 weeks were delivered by Caesarean section. The premature onset of labour was associated with a breech presentation in 3 cases and ante-partum haemorrhage in 4 cases. The indications for section were placenta praevia (2), ante-partum haemorrhage following attempted version (1), concealed accidental haemorrhage with foetal distress (1), uterine inertia (1), and previous repair of congenital recto-vaginal fistula (1).

(5) *In labour, at term, no delay.* Five patients had Caesarean section in labour, without any suggestion of uterine inertia, 2 were known cases of disproportion; these cases had been expected to have elective sections. Two of the sections were occasioned by foetal distress and the remaining case was one of breech presentation where the cervix became fully dilated but the breech did not descend.

(6) *In labour, at term, early delay.* There were 3 patients, each with minor degrees of disproportion, who had Caesarean section in labour (1 for delay, 2 for foetal distress) after minimal cervical dilation had been achieved. The durations of these labours were 17 hours (cervix 2 cm.), 19 hours (cervix 2 cm.) and 23 hours (cervix 1 cm.).

(7) *In labour at term, late delay.* Six patients had Caesarean section operations following prolonged labour, 5 for delay in the first stage and 1 for foetal distress. The durations of these labours were 41, 42, 47, 49, 50 and 91 hours, and the dilation of the cervix reached 6, 7, 7, 7, 6 and 6 cm. respectively, before operative delivery was decided upon.

Pre-eclampsia. Patients with pre-eclampsia were excluded from the present series in view of the known electrolyte disturbances occurring in this condition. A strict definition of the condition was applied, including all patients whose diastolic blood pressure was consistently above 85 in the last few weeks of pregnancy.

Site of biopsy. In the cases classified as normal uterus and in those cases where specimens were obtained from the uterus in early pregnancy, all the biopsies considered in the present work were taken from the *corpus uteri*, that is, from that part of the uterus lying above the level of the internal os. They are sub-divided into *upper*, which refers to approximately the upper two-thirds of the corpus, and *lower*, which refers to the lower third of the corpus, that is, to that part of the uterus which will eventually form part of the lower segment.

With the biopsies taken at Caesarean section, those specimens taken from the edge of a lower segment incision are referred to as *lower segment* whether or not the patient was in labour. In the few cases where specimens from the upper part of the uterus were available, they are referred to as *upper segment*, whether they came from the mid-part of the uterus or from the fundus.

Results

Normal Uterus

The electrolyte composition of the normal non-pregnant myometrium is shown in Table I, column 1. The water content corresponds to 80 per cent of the wet weight of the tissue, and of this three-quarters is extracellular. The large extracellular compartment comprises six-tenths of the tissue volume. The *concentration* of water

TABLE I

	Normal Uterus (Non-pregnant)		Skeletal Muscle (Mokotoff *et al.*, 1952)
	Upper Part	Lower Part	
Total water (g./kg. wet tissue)	795 ± 9·5 (5)	793 (1)	725
Total water (g./100 g. dry solids)	389 ±23 (5)	383 (1)	356
Extracellular water (g./100 g. dry solids)	293 ±21 (5)	301 (1)	56
Intracellular water (g./100 g. dry solids)	96 ±27 (5)	83 (1)	296
Intracellular water concentration (g./kg. I–C. phase)	490 ±65 (5)	458 (1)	743
Extracellular phase (g./100 g. dry solids) (=Chloride space)	295 ±22 (5)	304 (1)	57
Total chloride (m.–eq./100 g. dry solids)	35·0± 3·3 (5)	36·6 (1)	6·9
Total sodium (m.–eq./100 g. dry solids)	42·5± 2·3 (5)	42·6 (1)	11·5
Total potassium (m.–eq./100 g. dry solids)	29·6± 3·6 (5)	31·1 (1)	46·6
Total calcium (m.–eq./100 g. dry solids)	6·1± 3·3 (4)	10·0 (1)	—
Total magnesium (m.–eq./100 g. dry solids)	4·7± 3·1 (4)	7·7 (1)	7·8
Intracellular sodium (m.–eq./100 g. dry solids)	1·2± 2·6 (5)	1·9 (1)	3·5
Intracellular potassium (m.–eq./100 g. dry solids)	28·4± 3·6 (5)	30·0 (1)	44·1
Intracellular calcium (m.–eq./100 g. dry solids)	5·4± 3·2 (4)	9·4 (1)	—
Intracellular magnesium (m.–eq./100 g. dry solids)	4·4± 2·9 (4)	7·3 (1)	6·8

Note: Limits given in the first column are standard deviations. Bracketed figures represent number of cases.

inside the cells appears to be 490 grams per kilogram of intracellular phase, though in fact it is probably higher, since the solids of the so-called intracellular phase consist in part of organized structures such as the cell membrane.

The large extracellular space contains 97 per cent of the sodium in the tissue; the calculated intracellular sodium amounts to only 1·2 m.–eq./100 g. dry tissue. Potassium is very largely an intracellular ion, and the calculated intracellular potassium is 28·4 m.–eq./100 g. dry tissue, which represents 90 per cent of the total potassium. Calcium and magnesium are largely (89 per cent and 94 per cent respectively) in the intracellular phase. These ions may of course be in part incorporated in organized structures.

Table I, column 2, shows the composition of a single specimen from the lower third of the *corpus* of a normal uterus; the results do not differ significantly from those of the upper two-thirds of the *corpus uteri* in any particular. The mean results for the upper part of the corpus shown in Table I, column 1, have therefore been taken as typical of the myometrium of the normal non-pregnant uterus, and are used as a basis for comparison in the remainder of the work.

The composition of the myometrium is also compared with that of skeletal muscle in Table I, the data for skeletal muscle having been computed from values given by Mokotoff *et al.* (1952). The main differences between the composition of the two tissues are directly related to the very much larger extracellular space in the uterus. In skeletal muscle the extracellular space represents only one-ninth of the tissue, while in uterus six-tenths of the tissue is extracellular. This accounts for the higher content of the extracellular ions, sodium and chloride, found in myometrium and the smaller content of the intracellular ion, potassium. When the intracellular phases of the two tissues are compared it will be seen that the cation levels in the uterine muscle approach those in the skeletal muscle fibre, though the latter contains much more water.

Changes in the Electrolyte Composition of the Uterus During Normal Pregnancy and Labour (Tables II and III)

Water. During pregnancy the growth of the

TABLE II

	Lower Part of Corpus Uteri		Upper Part of Corpus Uteri	
	Early Pregnancy	At Term (Not in labour)	Early Pregnancy	At Term (Not in labour)
Total H_2O (g./kg. wet) ..	826 ±13 (6)	818 ±10 (5)	824 ±13 (5)	828 ± 8 (2)
Total H_2O (g./100 g. dry) ..	478 ±42 (6)	450 ±30 (5)	470 ±39 (5)	484 ±26 (2)
E–C H_2O (g./100 g. dry) ..	354 ±60 (6)	299 ±22 (5)	325 ±51 (5)	297 ±45 (2)
I–C H_2O (g./100 g. dry) ..	125 ±27 (6)	151 ±37 (5)	146 ±33 (5)	188 ±19 (2)
I–C H_2O concentration ..	558 ±50 (6)	602 ±64 (5)	592 ±54 (5)	655 ±21 (2)
E–C phase (g./100 g. dry) ..	357 ±61 (6)	302 ±23 (5)	328 ±52 (5)	300 ±46 (2)
Total Cl. (m.–eq./100 g. dry)	41·9± 7·1 (6)	36·1± 2·5 (5)	39·2± 5·9 (5)	35·3± 4·6 (2)
Total Na. (m.–eq./100 g. dry)	55·8± 7·7 (6)	48·3± 5·9 (5)	51·1± 7·9 (5)	52·1± 9·6 (2)
Total K. (m.–eq./100 g. dry)	33·1± 3·6 (6)	30·4± 6·1 (5)	34·3± 3·8 (5)	40·3± 3·9 (2)
Total Ca. (m.–eq./100 g. dry)	4·2± 1·7 (5)	6·7± 2·7 (4)	3·9± 1·6 (4)	13·2±10·5 (2)
Total Mg. (m.–eq./100 g. dry)	5·2± 1·9 (5)	5·1± 0·2 (4)	4·5± 1·1 (4)	10·3± 8·2 (2)
I–C. Na. (m.–eq./100 g. dry)..	6·0± 1·3 (6)	6·3± 3·2 (5)	5·5± 3·5 (5)	12·0± 4·1 (2)
I–C. K. (m.–eq./100 g. dry) ..	31·7± 3·7 (6)	29·3± 6·1 (5)	32·9± 4·1 (5)	39·0± 3·8 (2)
I–C. Ca. (m.–eq./100 g. dry)	3·4± 1·7 (5)	5·9± 2·7 (4)	3·1± 1·7 (4)	12·5±10·4 (2)
I–C. Mg. (m.–eq./100 g. dry)	4·8± 1·9 (5)	4·7± 0·3 (4)	4·2± 1·2 (4)	9·9± 8·0 (2)

Note: Designations of constituents and units, here abbreviated, correspond to those given in full in Table I. Standard deviations and number of cases are indicated.

TABLE III

	Normal Labour	Uterine Inertia	
		Delay Early in First Stage	Delay Late in First Stage
Total H_2O (g./kg. wet)	826 ± 10 (5)	832 ± 24 (3)	841 ±17 (6)
Total H_2O (g./100 g. dry)	477 ± 32 (5)	505 ± 92 (3)	534 ±74 (6)
E–C H_2O (g./100 g. dry)	375 ± 57 (5)	364 ±168 (3)	427 ±67 (6)
I–C H_2O (g./100 g. dry)	102 ± 52 (5)	142 ± 84 (3)	107 ±20 (6)
I–C H_2O concentration	488 ±118 (5)	551 ±177 (3)	510 ±45 (6)
E–C phase (g./100 g. dry)	377 ± 57 (5)	367 ±170 (3)	431 ±68 (6)
Total Cl. (m.–eq./100 g. dry)	43·8± 7·9 (5)	43·6± 18·3 (3)	51·7± 7·8 (6)
Total Na. (m.–eq./100 g. dry)	60·6± 17·6 (5)	59·4± 23·0 (3)	69·1±10·3 (6)
Total K. (m.–eq./100 g. dry)	29·6± 7·3 (5)	29·1± 12·8 (3)	27·0± 6·4 (6)
Total Ca. (m.–eq./100 g. dry)	6·2± 1·5 (2)	6·8± 4·3 (3)	3·8± 0·6 (6)
Total Mg. (m.–eq./100 g. dry)	4·9± 0·6 (2)	6·9± 1·8 (3)	5·5± 1·2 (4)
I–C Na. (m.–eq./100 g. dry)	8·9± 19·8 (5)	8·5± 3·1 (3)	9·7± 3·3 (6)
I–C K. (m.–eq./100 g. dry)	27·9± 7·0 (5)	27·0± 13·4 (3)	25·4± 6·0 (6)
I–C Ca. (m.–eq./100 g. dry)	5·5± 1·7 (2)	6·0± 3·9 (3)	2·7± 0·6 (6)
I–C Mg. (m.–eq./100 g. dry)	4·6± 0·8 (2)	6·4± 2·0 (3)	4·9± 1·1 (4)

Notes: 1. All specimens from the lower segments.
2. Constituents and units, here abbreviated, correspond to Table I.
3. Standard deviations and numbers of cases are indicated.

uterus is known to be accompanied by a relative increase in its water content (Treite, 1938). The present observations indicate the distribution of this excess water within the myometrium and that there are two distinct components to the change. Firstly, a transient increase in extracellular space and extracellular water occurs during the first few months of pregnancy. Secondly, a progressive increase in intracellular hydration takes place throughout pregnancy. Thus, after 3 to 5 months of pregnancy, the extracellular space has changed from 295 g./100 g. solids to 357 g./100 g. solids, an increase of 21 per cent. The concomitant increase in extracellular water accounts for two-thirds of the total change in uterine water during this period. As the uterus increases in size during the remaining months of pregnancy, the myometrial cells grow faster than the extracellular space. Consequently the proportion of the latter decreases in this period. At term the extracellular space occupies 302 g./100 g. solids, a situation which does not differ significantly from that in the non-pregnant uterus.

In contrast, the increase in intracellular water is progressive through pregnancy, from 96 g./100 g. solids in the non-pregnant uterus, to 125 at 3 to 5 months and 151 at term, a total of 57 per cent. This is not only a consequence of cellular growth, but an actual increase in cellular hydration occurs, the calculated concentration of water in the intracellular space rising from 490 g./kg. intracellular phase to 558 after 3 to 5 months and to 602 at term.

The progressive increase in intracellular water found in biopsies from the lower part of the *corpus uteri* is paralleled by a similar change in the upper part of the uterus.

When myometrium from patients at term but not in labour is compared with myometrium from patients in apparently normal labour, it appears that in the latter the volume of the myometrial cells is reduced, with loss of intracellular water. Comparison of Table II, column 2, with Table III, column 1, shows that the myometrial extracellular space is increased ($P<0{\cdot}05$) with a corresponding increase in extracellular water ($P<0{\cdot}05$) while the intracellular water concentration has fallen ($P<0{\cdot}1$) when the patient is in the first stage of labour. These findings are based on biopsies taken from the lower segment. We have had no opportunity to obtain specimens from the upper segment of the uterus in normal labour, and it is thus not clear whether or not these changes occur in the lower segment only, or in the whole uterus.

The observations on water content of the uterus are summarized in Figure 1.

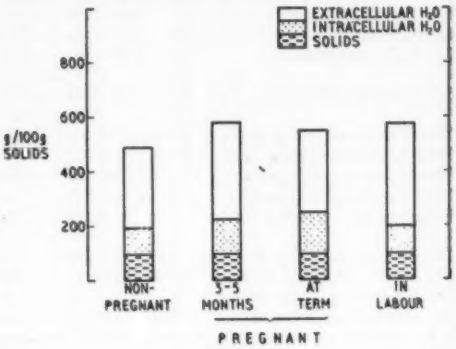

FIG. 1

Myometrial water in normal pregnancy and labour.

Chloride. No changes were found between the values for chloride content of the uterus per 100 g. solids in normal pregnancy or normal labour.

Sodium. There is an increase in the sodium content of the uterus during the early months of pregnancy. Though the total increase of some 13 m.-eq./100 g. solids is distributed between the two phases, the rise in calculated intracellular sodium from 1·2 to 6·0 m.-eq./100 g. solids is proportionately much greater than that in extracellular sodium, which is merely part of the expansion of the extracellular phase occurring at this time. The changes in the lower part of the corpus uteri appear to be paralleled by an increase to 5·5 m.-eq./100 g. solids in the cells of the upper part of the uterus ($P<0{\cdot}1$), and there is thus a generalized retention of sodium in the myometrial cells. No further rise was detected during the latter months of pregnancy, the lower segment cells containing 6·3 m.-eq./100 g. solids at term. An apparent further increase occurring in the mean sodium content of the cells of the upper segment is not significant.

No change in the uterine sodium levels was detected in normal labour.

Potassium. In cases of normal pregnancy and labour, no change in total or intracellular myometrial potassium levels was detected when the values were compared with those in normal non-pregnant uterus.

Intracellular sodium and potassium concentrations. The rise in uterine intracellular sodium per 100 g. solids which occurs in pregnancy without alteration in the corresponding value for potassium may be considered in relation to the observed rise in intracellular water (Fig. 2).

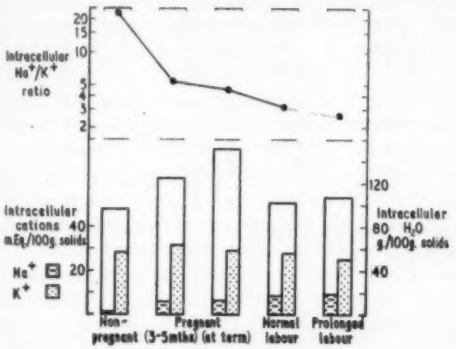

FIG. 2

Myometrial intracellular electrolytes in normal pregnancy and labour and in prolonged labour.

In conjunction, these changes could reflect either a steady or a rising sodium concentration in the protoplasm together with an actual fall in potassium concentration. In the absence of any information as to the proportions of the ions which are bound to intracellular structures, it is not possible to be sure of this.

More reliance can be placed on the observation that the myometrial intracellular potassium/sodium ratio falls during normal pregnancy, with a further fall in normal labour (Fig. 2).

Calcium and Magnesium. We were unable to detect any alterations in the total or calculated intracellular uterine levels of calcium or magnesium during normal pregnancy and labour.

Uterine Inertia and Long Labour (Table III)

The cases of delay in labour fell into two groups, those which had been in active labour for about 20 hours without achieving more than 2 cm. of cervical dilation, and those who had been in labour for more than 24 hours and had Caesarean section for failure to progress or foetal or maternal deterioration at a time when the cervix was more than half dilated. The first group therefore consisted of patients where delay occurred early in the first stage of labour and might be expected to reflect any changes pathognomonic of, and perhaps causal of uterine inertia. In the second group, containing the true cases of prolonged labour, it would be expected that the effects of prolonged maternal and uterine activity would be superimposed on any changes characteristic of uterine inertia *per se*.

Delay early in labour. We were unable to detect any differences when the electrolyte composition of biopsies from the lower uterine segment of patients in this group were compared with biopsies from patients in normal labour.

Delay late in labour. The only change in electrolyte composition found in these cases was a fall in tissue calcium. The mean calcium content was 6·0 m.-eq./kg. wet tissue in prolonged labour compared with 11·0 m.-eq./kg. in normal labour ($P<0·05$). In terms of dry tissue, the mean level was 3·8 m.-eq./100 g. solids in prolonged labour compared with 6·2 m.-eq./100 g. in normal labour ($P<0·1$). The majority of the tissue calcium appears to be in the intracellular phase, and there was a corresponding difference in calculated intracellular calcium levels ($P<0·1$).

Cort and Cort (1957) consider that uterine intracellular potassium is low in long labour; in the present series of prolonged labours the mean intracellular potassium was slightly reduced, 25·4 m.-eq./100 g. solids compared with 27·9 m.-eq./100 g. solids in normal labour (see Fig. 2); our difference was not significant.

There was no evidence of water or salt depletion in the uterus in prolonged labour in the present series of patients who were, of course, given parenteral fluids when indicated.

TABLE IV

	Premature Labour (No Ante-partum Haemorrhage)	Premature Labour Following Ante-partum Haemorrhage	Not in Labour Following Ante-partum Haemorrhage	Not in Labour Following Attempted Surgical Induction
Total H_2O (g./kg. wet)	828 (1)	827 ± 8 (4)	820 ± 9 (6)	830 ±13 (4)
Total H_2O (g./100 g. dry) ..	482 (1)	478 ± 26 (4)	458 ± 28 (6)	492 ±44 (4)
E–C H_2O (g./100 g. dry) ..	326 (1)	381 ± 42 (4)	368 ± 75 (6)	320 ±36 (4)
I–C H_2O (g./100 g. dry) ..	156 (1)	97 ± 59 (4)	91 ± 64 (6)	172 ±26 (4)
I–C H_2O concentration	617 (1)	468 ±118 (4)	427 ±199 (6)	638 ±33 (4)
E–C phase (g./100 g. dry) ..	329 (1)	385 ± 42 (4)	371 ± 76 (6)	323 ±36 (4)
Total Cl. (m.–eq./100 g. dry) ..	37·1±0·4 (2)	44·7± 3·9 (4)	42·9± 9·3 (6)	37·3± 4·8 (4)
Total Na. (m.–eq./100 g. dry) ..	49·6±2·2 (2)	57·6± 6·9 (4)	58·4± 15·9 (6)	59·0±11·2 (4)
Total K. (m.–eq./100 g. dry) ..	29·1±7·2 (2)	33·0± 5·9 (4)	28·3± 6·5 (6)	38·3± 7·1 (4)
Total Ca. (m.–eq./100 g. dry) ..	6·2 (1)	4·3± 0·8 (2)	7·6± 3·1 (3)	8·4± 4·4 (3)
Total Mg. (m.–eq./100 g. dry) ..	5·9 (1)	4·3± 2·6 (2)	5·0± 0·1 (2)	6·7± 2·9 (3)
I–C Na. (m.–eq./100 g. dry) ..	3·8 (1)	4·2± 6·2 (4)	7·8± 17·4 (6)	15·4±11 (4)
I–C K. (m.–eq./100 g. dry) ..	27·9 (1)	31·4± 5·8 (4)	26·8± 6·3 (6)	37·1± 7·3 (4)
I–C Ca. (m.–eq./100 g. dry) ..	5·5 (1)	3·4± 0·6 (2)	6·9± 3·0 (3)	7·6± 4·4 (3)
I–C Mg. (m.–eq./100 g. dry) ..	5·6 (1)	3·9± 2·5 (2)	4·5± 0·3 (2)	6·3± 2·7 (3)

Notes: 1. All specimens from the lower segment.
2. Constituents and units, here abbreviated, correspond to those in Table I.
3. Standard deviations and numbers of cases are indicated.

Premature Onset of Labour (Table IV)

Two cases, who went into labour at 37 weeks or before but had not had ante-partum haemorrhage, were studied. When the biopsies were compared with those from patients at term but not in labour, the only clear difference in electrolyte content was a slightly elevated total and intracellular magnesium content in one of the cases of premature labour. When these two prematurely active uteri were compared with uteri in normal labour at term, no statistically valid differences were detected.

Ante-partum Haemorrhage (Table IV)

Comparison of cases of premature onset of labour precipitated by ante-partum haemorrhage with the above group suggested that the uterine calcium levels were reduced after the haemorrhage. Minor changes suggestive of re-distribution of tissue water with some reduction in cell water were also observed. This is of interest in relation to the observations of Daniel and Boyes (1957) that water loss from the intracellular phase of the myometrium is associated with endometrial bleeding.

No differences were detected in cases starting labour as a consequence of ante-partum haemorrhage, compared with those where the haemorrhage was not followed by spontaneous labour.

Failed Induction of Labour (Table IV)

No abnormality of electrolyte composition was found in specimens from patients who failed to go into labour following surgical induction at term.

Red Blood Cell Electrolytes

Where possible, red blood cell sodium, potassium and chloride were estimated, with a view to seeing whether or not any changes occurring in the uterus were paralleled in other cells. We were in fact only able to detect (1) a lower sodium level in patients who had an ante-partum haemorrhage and went into labour

when these were compared with similar patients who did not go into labour, (2) a high chloride level in one case of failed induction of labour.

These changes did not correspond to concurrent changes in uterine electrolytes. Daniel and Bass (1956) have pointed out that the mechanism of electrolyte regulation in smooth muscle differs in some ways from that in other tissues.

Discussion

We have been unable to find in the literature any series of analytical figures strictly comparable with our findings in normal non-pregnant human uterus, shown in Table I. The two specimens of normal uterus studied by Kochman and Kruger (1926) were autopsy material, and, as Winkler (1935a) found, electrolyte composition of specimens obtained at autopsy differs from that of fresh tissue obtained by biopsy. Further, all the observations made before the present decade suffered from lack of simple and accurate analytical methods for sodium and potassium. In fact, Kochman and Kruger's data show a slightly lower water content, and lower values for sodium and potassium than those found in the present work. Our data for calcium, magnesium and chloride are in agreement with those of Kochman and Kruger. The series of nine specimens analyzed for potassium and calcium by Winkler (1935a) gave a very wide range of results which includes our mean values for potassium. Winkler's results for calcium range from 8 to 50 m.-eq./100 g. dry tissue, being sufficiently high in some cases to render the methods employed open to suspicion; our mean value lies at the lower extreme of this range. Treite (1938) gives analyses of four specimens of normal uterus, three of them having been obtained at laparotomy. The values for water, sodium and potassium do not differ significantly from those found in the present series, but the figures given for calcium and magnesium are lower than any found in our cases.

The single specimen studied by Manery and Hastings (1939) and quoted by Manery (1954) gave results for water and potassium in agreement with our findings but had a slightly lower total chloride content. Parvianen, Soiva and Ehrnrooth (1950) studied a uterus from a woman of 57. Their results for sodium, potassium and chloride, though of the same general order as our values, showed differences which can perhaps be attributed to the fact that the uterus was atrophic, and possibly pathological as well. Daniel (1955) notes that the sodium content of uterus from various species, including human, varied between 40 and 100 m.-eq./kg. wet tissue, a range that includes our values.

The specimens studied by Daniel and Boyes (1957) and the "normal" uteri used by Cort and Cort (1957) were obtained at hysterectomy, and were hence presumably pathological. As we have previously pointed out (Hawkins and Nixon, 1957a) the electrolyte content of such specimens can differ from that of non-pathological uterus. However, these authors used flame photometry to estimate sodium and potassium and in general their findings are in fair agreement with our observations.

Our observations that in the myometrium the majority of the calcium and magnesium is intracellular is in agreement with the findings of Scott (1940) who examined preparations of other smooth muscle tissues using the electron microscope.

The Uterus in Normal Pregnancy

There is again a lack of strictly relevant data available on the electrolyte content of the uterus during pregnancy. Winkler (1935a) studied total potassium and calcium levels in specimens of human uterus. His figures suggest that some increase in tissue potassium content may have occurred during pregnancy, but the scatter of the results is so wide and the methods available at that time were so much less reliable than those used now that comparison with modern data is difficult. Winkler's actual figures for calcium are very high. They suggest no trend during pregnancy, which is in agreement with our findings. Treite (1938) found an elevated water content at term, and also some rise in potassium content, but most of his cases were either autopsy material or from patients in abnormal pregnancy or labour. Treite's values for calcium and magnesium show no

definite trend through pregnancy. The single specimen from an elective Caesarean section analyzed by Parvianen, Soiva and Ehrnrooth (1950) gave results for total potassium and chloride which do not differ significantly from our mean values. A lower result for sodium was obtained in this case, but flame photometric methods were not used.

The results for a rather heterogeneous group of 8 cases studied by Daniel and Boyes (1957), including 3 specimens from uteri in early pregnancy, are in rough agreement with our findings with respect to total water, sodium, potassium, and chloride contents and also with respect to extracellular space estimates.

Thus, the available data in the literature, while indicating the general order of the electrolyte levels in the uterus during pregnancy, casts little light on any changes which may occur in consequence of, and during pregnancy. We therefore propose to discuss myometrial water and electrolytes in pregnancy primarily in terms of the results of the present work.

Seitchik and Alper (1956) studied the increase in total body water which occurs in normal pregnancy. They could find no evidence of selective increase in hydration in any of the body water compartments. More differential processes appear to be involved in the increase in hydration of the uterus.

The expansion of the extracellular phase of the uterus which is found in the early months of pregnancy is a change which may be attributed to increased oestrogen influence. At this time in pregnancy, the production of oestrogen, as evidenced by urinary excretion, is increased (Zondek, 1931, p. 198; Smith, Smith and Pincus, 1938) as are the circulating blood levels (see Zondek, 1931, p. 201; Preedy and Aitken, 1957) and it is known from animal experiments that administration of oestrogen produces an increase in the extracellular phase of the uterus (Talbot *et al.*, 1940; Horvath, 1954).

It might be considered that the increased secretion of the adrenal cortex hormones which occurs in pregnancy (Venning, 1946; Tobian, 1949; Parvianen, Soiva and Vartianen, 1950; Jailer, 1951; Lloyd *et al.*, 1952; Venning, Singer and Simpson, 1954) plays a part in producing a rise in the myometrial extracellular phase. It is unlikely that aldosterone itself is a primary factor. Rinsler and Rigby (1957) suggest that the increased output of aldosterone in pregnancy is merely a secondary effect, compensating for the passage of water and sodium into the maternal and foetal cells by increased renal re-absorption. It is also unlikely that the other corticoids are of major importance in producing the increase in extracellular space at 3 to 5 months, since Venning (1946) has shown that the output of these hormones is in fact transiently reduced at this stage of pregnancy.

In view of Horvath's observation that administration of progesterone did not produce any increase in myometrial extracellular water in animal experiments it is unlikely that this hormone is responsible.

By the time that the end of pregnancy is reached, the measured myometrial extracellular space becomes reduced again to the same proportions as in the non-pregnant uterus. This is probably due to cellular growth having taken place to a degree corresponding to the expansion of the extracellular compartment. The withdrawal of oestrogen influence which is generally believed to occur about the time of the onset of labour may also be involved.

The progressive increase in myometrial intracellular water which occurs in pregnancy is of interest since it is accompanied by a progressive increase in intracellular water concentration, that is, a true change in cellular hydration with consequent dilution of the protoplasm of the myometrial cells. Such a response has been demonstrated to occur specifically in the uterus, without corresponding changes in other organs, following the administration of oestrogen in rats (Talbot *et al.*, 1940) and would appear to be part of the process of cellular growth in response to hormonal influence.

The rise in intracellular sodium we have observed during pregnancy is in agreement with the findings of Cort and Cort (1957) though the absolute levels quoted by these authors differ slightly due to the use of a different assumption in the determination of extracellular space. Our data suggests that in the lower part of the uterus, at least, the rise is completed in the early months of pregnancy and we are inclined to attribute the effect to the same mechanism that

we have suggested is responsible for the increase in extracellular space which occurs at this time. That is, to increased oestrogen influence and possibly also to the effect of adrenal cortex secretions. In contrast to Cort and Cort (1957) we find no actual loss of potassium from the cells of the myometrium in pregnancy. The difference may be due to the use by these authors of presumably pathological uterus obtained at hysterectomy to determine the non-pregnant level. A factor which could cause a loss of potassium from smooth muscle cells, and hence an artificially low value in specimens from Caesarean section, is the administration of smooth muscle stimulants such as oxytocic drugs, before taking a biopsy—an artefact we have avoided in the present work. Our findings of an increase in intracellular sodium without concurrent loss of potassium from the cells during the early months of pregnancy suggests the influence of oestrogens rather than that of the adrenal cortex hormones, since the latter cause a generalized loss of cellular potassium (Eliel *et al.*, 1951), while oestrogens have no such effect, either on the body as a whole (Preedy and Aitken, 1956) or on the uterus (Talbot *et al.*, 1940; Horvath, 1954).

Myometrial intracellular water increases in pregnancy concurrently with cellular sodium. The accurate determination of absolute values for intracellular sodium is so dependent on the assumption used in measuring extracellular space, it is not clear whether or not these changes are in proportion, that is, whether or not the apparent intracellular sodium concentration is maintained constant. As in the lower segment specimens cell water continues to increase during the latter months of pregnancy while intracellular sodium showed no further rise during this time, one may deduce that there is, in fact, a slight fall in the concentration of sodium in the cells at the end of pregnancy. Potassium concentration in the intracellular fluid is probably reduced during pregnancy in consequence of the increased hydration of the cells, but the extent of this reduction is difficult to assess without information regarding the proportion of potassium bound to structures in the intracellular phase. In the absence of clear evidence of actual loss of potassium from the cells, we cannot agree with Cort and Cort (1957) that this fall in potassium concentration represents a pathological depletion of the cell potassium but consider it more likely to be a physiological consequence of hormonal influences and uterine growth.

It is of interest to note that such a fall in concentration of cellular potassium could be related to the increased excitability of the uterus in the later months of pregnancy. The membrane potential of muscle cells is a function of the intracellular/extracellular potassium gradient, and the excitability of muscle is increased by a low membrane potential. Evidence that these phenomena occur in the uterus under the influence of oestrogen has been deduced by Csapo (1956a, b), though as Woodbury and McIntyre (1954) demonstrated, the relation is not so simple in the myometrium as it is in the frog muscle. A fall in intracellular potassium concentration such as that occurring late in pregnancy would be expected to produce a decrease in the gradient and consequently in the membrane potential. Thus the threshold of the uterus to stimuli would be lowered, facilitating such activity as Braxton-Hicks contractions, and perhaps the onset of labour itself.

The Uterus in Labour

With the exception of the present investigation, the publication of Cort and Cort (1957) and a very few analyses of single specimens, data on the uterine electrolytes in normal labour is lacking. We were unable to obtain confirmation of Cort and Cort's observation that a small amount of potassium is lost from the cells in normal labour. As has already been pointed out (Hawkins and Nixon, 1957a), the group of cases in labour described by Cort and Cort contained a number of patients where the head had failed to engage and a trial labour had failed. The reduction in mean intracellular potassium found in these cases may have been exaggerated by uterine inertia.

The principal change in normal labour found in the present study was an increase in extracellular space associated with a loss of water from the myometrial cells. On the basis of our data it is not possible to distinguish clearly

between changes immediately preceding the onset of labour and changes consequent on entry into the first stage. It seems likely that the effect is due to an alteration in morphology consequent upon the activity of the myometrium, that is, to the formation of the lower segment. The changes are not characteristic of any hormonal change which may be thought to anticipate labour.

Prolonged Labour

Winkler (1935b) analyzed specimens of uterus from three cases of uterine inertia, finding a reduction in potassium content. One of the 3 cases of uterine inertia studied by Treite (1938) showed a low potassium content; in one of the remaining cases the figure for potassium is of doubtful authenticity. Since 95 per cent of myometrial potassium is intracellular, the result suggests that loss of cellular potassium from the uterus can occur in prolonged labour. The recent observations of Cort and Cort (1957) support this view. While in the present series of cases we also found a slight reduction in intracellular potassium in prolonged labour, we were unable to verify our findings statistically. There seems to be no evidence in the present study, or in Treite's (1938) 3 cases, of dehydration or sodium loss from the myometrial cells, and Cort and Cort (1957) found actual increases in myometrial water and sodium in their cases of long labour.

We had hoped that our analyses of 3 specimens from patients with uterine inertia who had Caesarean section operations after only 20 hours in labour might have revealed some changes which could be interpreted as causative, but this was not the case. Comparisons of results from patients who did and did not go into labour following ante-partum haemorrhage or surgical induction, proved equally devoid of clues to the origin of uterine inertia. The observation of a slightly elevated tissue magnesium in one case of premature labour is probably a chance finding and the significance of the elevated intracellular water in one case of premature labour (Table IV, column 1) is offset by a similar finding in uterine inertia (Cort and Cort, 1957). Since the electrolyte changes that do occur in prolonged labour are found after many hours, it seems most likely that they are merely a consequence of prolonged labour.

The cause of the fall in total and intracellular myometrial calcium we have observed in prolonged labour is by no means clear to us. It is conceivable that this effect is a consequence of the drain on fixed base occasioned by acidosis.

There are three mechanisms which could be responsible for the loss of myometrial potassium in prolonged labour. The first, suggested by Cort and Cort (1957), is that since potassium binding in the cell is linked with glycogen storage, and West and Cervoni (1955) have demonstrated that myometrial glycogen levels are decreased by uterine contractions, the loss of potassium may be secondary to utilization of the myometrial glycogen stores. It is then suggested that the rise in cell water and sodium observed is secondary to local anoxia affecting sodium transport.

Secondly, loss of cellular potassium could be interpreted as due to a cumulative effect of the small potassium loss consequent on each uterine contraction. There is a fair amount of evidence that this mechanism is operative in smooth muscle and that sodium accumulation is another consequence (Parrot *et al.*, 1953; Born and Bülbring, 1956; Tobian and Fox, 1956; Macmillan and Vane, 1956). Thirdly, the changes could be accounted for by increased activity of the adrenal cortex during prolonged labour. As we have pointed out (Hawkins and Nixon, 1957b) the serum electrolyte and eosinophil changes occurring in prolonged labour can be attributed to adrenal cortex hypersecretion.

In the present state of our knowledge it would be rash to attempt to decide between these possible explanations, and all three mechanisms might well be involved.

The consequences of reduced cellular potassium, without loss of cell water, are not necessarily unfavourable. The fall in intracellular potassium concentration will result in a lowered K^+ concentration gradient across the cell membrane, and consequent increase in excitability. Thus in hypotonic uterine inertia, provided the patient is adequately hydrated, and the plasma potassium level remains normal, then myometrial potassium loss will accelerate

the course of labour. If the patient's plasma potassium level is allowed to fall, a process which tends to occur after about 36 hours in labour (Hawkins and Nixon, 1957b) then the beneficial effect of reduced myometrial potassium will be lost. It is therefore of some importance to maintain the plasma electrolytes of patients in prolonged labour by appropriate intravenous therapy.

Summary

(1) Analyses for water, chloride, sodium, potassium, calcium and magnesium were conducted on biopsy specimens of human myometrium. Intracellular levels of water and of the cations were computed using "chloride space" to measure extracellular space.

(2) The normal non-pregnant human myometrium has a large extracellular phase, occupying six-tenths of the tissue. The myometrial cells contain much less water than skeletal muscle fibres.

(3) During the first few months of normal pregnancy, the myometrial extracellular phase expands; in the remaining months of pregnancy differential growth of the two phases occurs in such a way that at term the normal proportions are restored.

(4) The myometrial cells become progressively more hydrated throughout a normal pregnancy. Intracellular sodium increases in pregnancy; no change in intracellular potassium (per 100 g. solids) was detected.

(5) It is considered that the above changes during normal pregnancy can be accounted for by increased oestrogen influence.

(6) In normal labour the proportion of the lower segment myometrium occupied by cells is reduced, with loss of intracellular water. This may be due to the formation of the lower segment.

(7) No differences in water or electrolyte composition were detected when biopsies taken from cases of uterine inertia after 17 to 23 hours of labour were compared with biopsies from patients in normal labour. The myometrium of patients who had been in labour 41 to 91 hours had a reduced total and intracellular calcium content; the mean intracellular potassium content was slightly reduced. It is thought that these changes in prolonged labour were a consequence, rather than a cause, of uterine inertia.

(8) Analyses of myometrium from a few cases of premature onset of labour, ante-partum haemorrhage, and failed induction of labour are given.

(9) The findings are compared with the results of earlier workers, and discussed in relation to the possible causes and consequences of the changes found.

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THE UTERINE ELECTROLYTES IN PRE-ECLAMPSIA

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WE have described the changes which occur in the electrolyte composition of the uterus in normal pregnancy and labour, and in prolonged labour (Hawkins and Nixon, 1958). The present report concerns the abnormalities of myometrial composition which are found in pre-eclampsia.

METHODS

Small biopsies of the myometrium of patients with pre-eclampsia were taken from the edges of either lower or upper segment uterine incisions at Caesarean section operations performed under general anaesthesia. At the same time specimens of heparinized blood were obtained by venepuncture. The subsequent treatment of the specimens, the analytical methods employed, and the computation of intracellular electrolyte levels, have already been described (Hawkins and Nixon, 1958).

The results were expressed per 100 g. dry tissue and averaged for each group of patients considered. The mean values shown in Table I are accompanied by standard deviations representing variation between patients. In order to assess abnormalities in the electrolyte composition of the uterus attributable to pre-eclampsia, the results were compared with those

TABLE I

Uterine Electrolytes in Pre-eclampsia

	At Term Not in Labour		Normal Labour	Prolonged Labour	Failed Induction
	Lower Segment	Upper Segment	Lower Segment	Lower Segment	Lower Segment
Total H_2O (g./kg. wet tissue)	831 ±10 (5)	828 ± 3 (4)	829 ± 8 (6)	826 ± 33 (3)	847 ±16 (4)
Total H_2O (g./100 g. dry solids)	495 ±38 (5)	483 ± 9 (4)	488 ±27 (6)	490 ±118 (3)	558 ±65 (4)
Extracellular H_2O (g./100 g. dry solids)	358 ±27 (4)	320 ±43 (4)	374 ±54 (6)	433 ±110 (3)	393 ±30 (4)
Intracellular H_2O (g./100 g. dry solids)	144 ±19 (4)	163 ±39 (4)	114 ±40 (6)	57 ± 14 (3)	165 ±36 (4)
Intracellular H_2O concentration (g./kg. I–C phase)	598 ±33 (4)	621 ±48 (4)	523 ±97 (6)	370 ± 60 (3)	627 ±54 (4)
Extracellular phase (g./100 g. dry solids) (=Chloride space)	361 ±27 (4)	323 ±43 (4)	378 ±55 (6)	438 ±112 (3)	397 ±30 (4)
Total chloride (m.eq./100 g. dry)	44·8± 2·9 (4)	40·2± 6·1 (4)	44·3± 5·3 (6)	53·1± 12·4 (3)	49·7± 3·2 (4)
Total sodium (m.eq./100 g. dry)	60·8± 5·7 (5)	52·8± 8·0 (4)	58·4± 8·8 (6)	70·8± 9·8 (3)	67·9± 6·6 (4)
Total potassium (m.eq./100 g. dry)	35·7± 6·6 (5)	35·9± 4·7 (4)	31·9± 5·5 (6)	26·0± 6·3 (3)	37·8± 8·8 (4)
Total calcium (m.eq./100 g. dry)	5·6± 1·0 (4)	9·3± 4·6 (4)	8·3± 4·3 (2)	8·7± 1·6 (3)	5·4± 1·2 (3)
Total magnesium (m.eq./100 g. dry)	5·4± 1·3 (4)	5·8± 1·5 (4)	7·2± 1·6 (3)	4·4± 1·0 (3)	5·6± 1·9 (3)
Intracellular sodium (m.eq./100 g. dry)	12·1± 4·6 (4)	10·3± 3·1 (4)	8·7± 9·4 (6)	9·0± 5·1 (3)	13·9± 4·8 (4)
Intracellular potassium (m.eq./100 g. dry)	34·2± 6·7 (4)	34·2± 3·8 (4)	30·5± 6·1 (6)	24·3± 5·9 (3)	36·2± 8·7 (4)
Intracellular calcium (m.eq./100 g. dry)	4·8± 1·2 (4)	8·6± 4·7 (4)	7·4± 4·5 (2)	7·7± 1·7 (3)	4·3± 1·2 (3)
Intracellular magnesium (m.eq./100 g. dry)	5·1± 1·3 (4)	5·3± 1·3 (4)	7·4± 0·6 (2)	3·9± 0·9 (3)	5·1± 1·9 (3)

Note: Standard deviations and numbers of cases are indicated.

obtained in the previous study (Hawkins and Nixon, 1958), which concerned only patients with no evidence of pre-eclampsia. For this comparison "t" tests were employed. In general, changes demonstrable at the P=0·05 level were considered significant.

Cases Studied

Patients whose diastolic blood pressure rose above 85 mm. Hg in the last few weeks of pregnancy were considered to have pre-eclampsia. All the cases selected on this basis had already been independently diagnosed as having pre-eclampsia in the antenatal clinic. The 16 patients studied included 2 whose pre-eclampsia was superimposed on essential hypertension and 1 patient where pre-eclampsia was superimposed on a mild sub-acute nephritis of several years standing.

The cases were grouped as follows:

(1) *At term, not in labour:* 6 patients between 38- and 42-weeks pregnant by dates had elective Caesarean section operations. Of these, 4 had mild pre-eclampsia (diastolic blood pressure 85–95), 1 had pre-eclampsia of moderate severity (diastolic blood pressure 95–105), and 1 had severe pre-eclampsia (diastolic blood pressure over 105). In addition to pre-eclampsia, the following indications for operative delivery were present: failed induction, minor disproportion, overdue, 1; failed induction, thought to be overdue, 1; failed induction, minor disproportion, bad obstetric history, 1; transverse lie at term, 1; partially detached retina during pregnancy, 1; premature rupture of membranes, prolapsed cord, 1.

(2) *In labour at term:* 6 patients had Caesarean section operations during labours where there was no evidence of inertia. Of these, 5 had mild, 1 moderately severe, pre-eclampsia. Additional indications for section were: previous prolapse repair, scheduled for elective section, 1; prolapsed cord, twins, 1; intra-partum infection, 1; foetal distress, breech, 1; foetal distress, occipito-posterior, 1; disproportion, failed forceps, 1.

(3) *Prolonged labour:* 3 patients had Caesarean section operations during labours where there was evidence of uterine inertia. Two had mild pre-eclampsia, 1 moderate. The durations of spontaneous labour were 36 hours (cervix 2 cm.), 73 hours (cervix 5 cm.), and 24 hours (cervix 7 cm.), respectively. The third case was a footling breech.

(4) *Failed induction.* In addition to the 3 patients mentioned above where medical and surgical procedures failed to initiate labour, 1 other case of moderate pre-eclampsia was included in this group.

Patients who had received oxytocic drugs shortly before the biopsies were taken were excluded from the present series as we have some evidence that these drugs cause alterations in the uterine electrolytes.

Results

Mean values for the electrolyte content of the myometrium are shown in Table I. The abnormalities found are discussed in relation to our previous findings in patients without pre-eclampsia (Hawkins and Nixon, 1958).

Pre-eclampsia at Term

Comparison of the lower part of the uterus of patients with pre-eclampsia at term but not in labour with normal non-pregnant uterus showed that in pregnancy complicated by pre-eclampsia the total water content increased by 27 per cent. This is greater than the increase of 16 per cent found in normal pregnancy. Thus, at term the pre-eclamptic myometrium contains 495 g. water per 100 g. solids. The excess water uptake in pre-eclampsia appears to be confined to the extracellular phase of the myometrium (Fig. 1) with consequent increase in the extracellular space measurement and a corresponding rise in total tissue chloride and sodium.

The principal intracellular abnormality found consisted of an elevated sodium level in the cells. Thus, in pregnancy complicated by pre-eclampsia, intracellular sodium rose from 1·2 m.-eq./100 solids to 12·1 m.-eq. at term, an increase which is double that found in normal pregnancy. This change was not accompanied by any increase in water content of the cells, and cellular hydration, as measured by the intracellular water concentration, was unchanged. It is therefore likely that there was

an increase in the actual concentration of sodium in the intracellular fluid.

The electrolyte composition of biopsies of the upper part of the uterus in pre-eclampsia is also shown in Table I and it will be seen that intracellular levels of sodium and potassium correspond closely to those in the lower segment. We had data from only 2 comparable uncomplicated cases, and were unable to verify statistically that changes similar to those seen in the lower segment in pre-eclampsia had taken place in the upper part of the uterus.

Red blood cells from the patients studied were also analyzed in a few cases. In agreement with the results of Nordenstrahl (1952), we were unable to detect any change in sodium, potassium or chloride contents attributable to pre-eclampsia.

Pre-eclampsia and Labour

In labour complicated by pre-eclampsia myometrial total and intracellular magnesium were higher than in uncomplicated labour ($P<0\cdot1$). This difference was due to a rise in intracellular magnesium occurring only in the former group ($P<0\cdot05$).

Pre-eclampsia and Prolonged Labour

The changes in electrolyte composition previously found in prolonged labour terminating a normal pregnancy were minimal, consisting of a fall in tissue calcium and some suggestion of a fall in intracellular potassium (Hawkins and Nixon, 1958). More marked changes were found in specimens from patients with pre-eclampsia who had prolonged labours. The data for these patients are shown in Table I, and indicate the correct trends; statistical validity for some of the changes was obtained only when they were considered per kg. wet tissue.

The changes in the myometrium found to develop in prolonged labour in patients with pre-eclampsia consisted of a transfer of water from the intracellular compartment, a loss of potassium from the cells, and a fall in total and intracellular magnesium.

The fall in intracellular water was from 114 to 57 g./100 g. solids, the latter being the lowest mean value we have recorded in any specimens of uterus. A corresponding increase in extracellular space and extracellular water occurred, reflected by increase in total tissue chloride and sodium. The loss of water from the myometrial cells was sufficient to cause a fall in the calculated concentration of water in the intracellular phase, and may reasonably be referred to as a cellular dehydration. We could find no evidence that this was accompanied by loss of sodium from the myometrial cells.

Intracellular potassium fell from a mean value of 34·2 m.-eq./100 g. solids before labour began to 24·3 m.-eq./100 g. in the course of these prolonged labours. This may be compared with a fall from 29·3 to 25·4 occurring in prolonged labour in patients without pre-eclampsia, and adds further support to the contention of Cort and Cort (1957) that depletion of myometrial intracellular potassium occurs in prolonged labour.

It is noted above that uterine total and intracellular magnesium were elevated in labour in pre-eclampsia. The fall in magnesium observed in prolonged labour in pre-eclampsia corresponds in magnitude to a loss of this excess magnesium.

Failed Induction of Labour

Medical and surgical induction had failed to initiate labour in three of the six cases of pre-eclampsia at term. In order to confirm our previous failure to find any electrolyte disturbance associated with failed induction, data was computed for cases of this type in the present series. The failure to respond to induction was not directly associated with any electrolyte abnormality in the uterus, in pre-eclampsia.

Intracellular Ions in Pre-eclampsia

The abnormalities of tissue water and intracellular ions observed in pre-eclampsia are summarized in Figures 1 and 2.

Some preliminary observations (Nixon and Smyth, 1957) had suggested that the intracellular potassium/sodium ratio might be elevated in pre-eclampsia. The present series of more highly selected cases and statistically evaluated results failed to confirm this. The intracellular potassium/sodium ratio is low in late pregnancy in pre-eclampsia, because of the increased sodium content of the cells, but in normal or

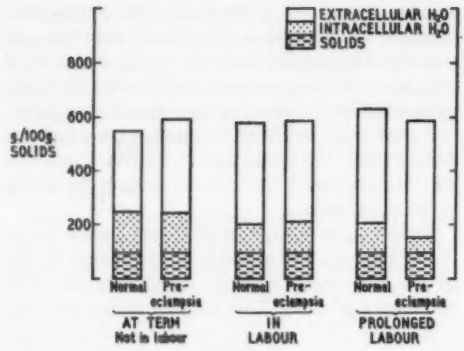

FIG. 1

Myometrial water in pre-eclampsia.

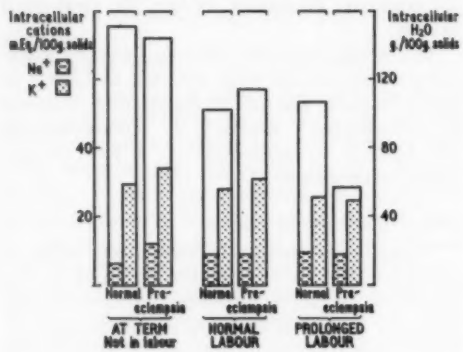

FIG. 2

Myometrial intracellular electrolytes in pre-eclampsia.

prolonged labour the ratio is unaffected by pre-eclampsia. The value of the ratio falls in prolonged labour in consequence of potassium loss from the myometrium.

DISCUSSION

The generalized disturbance of electrolyte metabolism which occurs in pre-eclampsia has been widely studied, and it is generally agreed that retention of water, sodium, potassium and chloride occurs. In particular the careful studies of Dieckmann and Pottinger (1955) suggest that the principal site of accumulation is the extracellular space. The present results indicate that the myometrium is involved in this expansion of the extracellular compartment.

The tendency of the myometrial cells to have an increased cell sodium level would appear to be a consequence more specific to the uterus, since Nordenstrahl (1952) found no such effect in red blood cells, while the results of Dieckmann and Pottinger (1956) do not suggest any abnormal accumulation of sodium in voluntary muscle or skin. The experiments of Daniel and Bass (1956) suggest that the mechanism controlling electrolyte balance in smooth muscle differs from that in skeletal muscle. In view of the observations of Talbot, Lowry and Astwood (1940) and Horvath (1954) on the effects of oestrogen and progesterone on the electrolytes of the uterus it would not be surprising to find even more specific mechanisms in this organ.

The failure of cell water to increase in the face of increased cell sodium, considered in conjunction with the rapid and severe myometrial cellular dehydration found in prolonged labour in patients with pre-eclampsia, suggests a marked abnormality of fluid transfer to and from the myometrial cells. Dieckmann and Pottinger (1955) invoke a similar defect to explain the abnormalities of total body fluid distribution.

Our findings also suggest that some abnormality of tissue magnesium occurs. Myometrial magnesium was high in pre-eclampsia at term and this elevation persisted in labour. In prolonged labour the excess magnesium associated with pre-eclampsia was lost.

It is possible that the electrolyte abnormalities of pre-eclampsia described may be related to disturbance of the hormonal regulation of pregnancy. Although Parvianen and his associates (Parvianen, Soiva and Vartiainen, 1950; Parvianen, Soiva and Ehrnrooth, 1951) have suggested that disturbed secretion of adrenal cortical hormones may be an aetiological factor, the balance of evidence is against this view. Though they observed changes in steroid excretion in pre-eclampsia, Venning, Singer and Simpson (1954) were not able to demonstrate any constant relations between steroid fractions excreted and the severity of the pre-eclampsia, and Rinsler and Rigby (1957) were unable to detect any change in aldosterone excretion which

could account for the sodium retention and other changes of pre-eclampsia. In fact, Rinsler and Rigby found a low aldosterone output in pre-eclampsia, presumably compensatory in nature.

Whilst capillary permeability is increased in pre-eclampsia (see Nordenstrahl, 1952, p. 15) this change is by no means a specific indication of altered adrenal function. More significant are the facts that circulating eosinophil count (Bernstein and de Andino, 1952; Kyank and Hass, 1953; Dawson, 1953), serum potassium (Tatum, 1954; Dieckmann and Pottinger, 1956), and red cell electrolytes (Nordenstrahl, 1952), are all unchanged in pre-eclampsia.

This is good evidence that there is no generalized change in adrenal function. The pattern of body electrolyte disturbance in pre-eclampsia, consisting of retention of water, sodium, potassium and chloride is not characteristic of altered adrenal influence neither is the distribution of these retained ions.

Further evidence that generalized adrenal cortex abnormality is not an aetiological factor in pre-eclampsia comes from the work of Jailer (1951) and of Dieckmann and Pottinger (1955). These authors demonstrated that the administration of quite large doses of adreno-corticotrophic hormone, cortisone or hydrocortisone were without either deleterious or beneficial effect on the clinical course of pre-eclampsia. Jailer (1951) also studied patients with Addison's disease during pregnancy and obtained evidence suggesting that the source of the increased adrenal steroid excretion in pregnancy was the placenta rather than the adrenal gland. If this is the case, then any changes in steroid excretion in pre-eclampsia may be merely secondary to alteration in placental function.

For the above reasons we are not inclined to consider the adrenal cortex as playing a part in the genesis of the abnormalities of myometrial electrolytes we have observed in pre-eclampsia.

Dalton (1954, 1957) has adduced evidence that lack of progesterone may be one of the important factors in the causation of pre-eclampsia, and Russell *et al.* (1957) have shown clearly that pregnanediol excretion is reduced in pre-eclampsia. In the past, progesterone therapy during pregnancy has suffered from the use of doses which are probably homoeopathic in comparison with the output of the placenta. Dalton's trial of more adequate doses of progesterone in the treatment of pre-eclampsia has given encouraging results.

Lack of progesterone implies relative preponderance of oestrogen activity. Both these hormones influence the uterine electrolytes. It is by no means easy to say whether or not such progesterone-oestrogen imbalance could account for the abnormalities of uterine electrolytes observed in pre-eclampsia. We are at the present time conducting experiments to determine the effects of these hormones on the uterine electrolytes during pregnancy.

Summary

(1) Analyses for water and electrolytes were conducted on biopsy specimens of human myometrium from patients with pre-eclampsia. Intracellular levels of water and of the cations were computed using "chloride space" to measure extracellular space.

(2) In pregnancy complicated by pre-eclampsia the myometrium gains more water than in normal pregnancy. The pathological increase in myometrial water is confined to the extracellular phase; there is a corresponding increase in the extracellular ions of the myometrium, sodium and chloride.

(3) The sodium content of the myometrial cells is increased in pre-eclampsia.

(4) Myometrial magnesium levels were higher during labour in patients with pre-eclampsia than in patients without this condition.

(5) Prolonged labour is associated with a severe loss of water from the myometrial cells in patients with pre-eclampsia, a change not seen in the uncomplicated cases of prolonged labour.

(6) The findings are discussed in relation to a possible hormonal aetiology of the electrolyte changes in pre-eclampsia. It is considered that a generalized abnormality of adrenal cortex secretion could not account for the changes observed in pre-eclampsia.

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OVARIAN ACTIVITY FOLLOWING HYSTERECTOMY

BY

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INTRODUCTION

GYNAECOLOGICAL surgeons may be said to be divisible into those who, when performing the operation of hysterectomy, make it part of their routine simultaneously to remove the ovaries, and those who endeavour, at least in the pre-menopausal patient, to conserve all possible ovarian tissue, unless gonadal pathology or pelvic malignant disease dictates for them a more radical course of action.

Protagonists of bilateral oöphorectomy offer two arguments in support of their practice. The first is that once the uterus has been removed ovarian atrophy and cessation of function soon follow, and the second is that removal of a woman's ovaries precludes the possibility of that particular patient developing, at a subsequent date, carcinoma of these organs.

Those whose policy it is to conserve the ovaries whenever possible usually attempt to justify their more cautious attitude by pleading a natural reluctance to excise tissue which has the appearance of being healthy and still functioning, adding perhaps a word of scepticism concerning the alleged early atrophy of the ovaries which is said by some to occur after hysterectomy has been performed. They sometimes give, as an additional reason for conservatism, their belief that oöphorectomy, when carried out on a woman during the reproductive period of life, by abruptly depriving her of the ovarian hormones, is likely to precipitate a more severe menopause than that which occurs as a consequence of the gradual physiological decline in ovarian activity which, they contend, ensues if the ovaries are left at operation.

Although this subject has aroused the curiosity of many workers (Sessums and Murphy, 1932; Burford and Diddle, 1936; Hendry, 1936; Bonney, 1937; Richards, 1951), only a handful of the many investigators have attempted to tackle the problem from more than one aspect, and most of the published work is weakened by a total neglect of controls.

It comes indeed as no surprise to discover that the American S. R. M. Reynolds (1949), in his book, *The Physiology of the Uterus*, devotes eight pages to the endocrinological effects of hysterectomy and that this section of the work, which contains eighty-three references, is summarized by the author as follows:

> "The effects of hysterectomy upon the ovary are today the subject of divided opinion despite an abundance of clinical and experimental consideration by eminent clinicians and investigators for more than sixty years."

It would appear, therefore, that neither those who remove, nor those who conserve the ovaries at hysterectomy do so from arguments that rest upon a sound foundation of established scientific fact.

That this should still be so is surely sufficient justification for yet another investigation of the problem, for the subject is not only of intrinsic scientific interest but also of considerable clinical importance.

GENERAL PLAN OF INVESTIGATION

In this piece of research three groups of subject were investigated. These were:

Group (*a*) consisting of twenty-four women who had undergone, prior to the menopause, the operation of hysterectomy with conservation of one or both ovaries.

Group (*b*) consisting of twenty-four women of comparable age and pelvic pathology who had undergone, prior to the menopause, the operation of hysterectomy with bilateral salpingo-oöphorectomy.

Group (*c*) consisting of fourteen women of comparable age, who had undergone neither operation but whose uteri and ovaries were still *in situ* and apparently functioning.

The problem of ovarian activity following hysterectomy was investigated by the following methods:

(1) By the menopausal index, i.e., by a mathematical assessment of the severity of the menopausal syndrome made on the basis of a points system.

(2) By the use of temperature records which, if they exhibited the diphasic pattern characteristic of the ovulating subject, might be considered as evidence of the persistence of ovulation following hysterectomy.

(3) By the use of urinary pregnanediol estimations designed to check the accuracy of the conclusions reached by means of the temperature records.

(4) By the use of vaginal smears stained to show evidence of cornification and therefore employed as an index of the oestrogenic activity of the conserved ovaries.

(5) By bio-assay of pituitary gonadotrophin.

The Methods of Investigation

First Investigation

It has long been realized that the menopause is frequently accompanied by a variety of symptoms of which a typical example is the vasomotor disturbances known as "hot flushes". That these are very probably related to a fall in oestrogen production by the ovary is suggested by the well-known fact that replacement therepy in the form of natural or synthetic oestrogens very frequently effects a diminution in the severity of the symptom, if not its complete abolition (Hawkinson, 1938; Bishop, 1947; Kupperman *et al.*, 1953). A similar response has been observed when oestrogens are given to the castrated subject (Bishop, 1938).

Although writers are not unanimous concerning which symptoms are to be regarded as distinctively menopausal, there is a considerable measure of agreement on the subject. An analysis of the menopause in one thousand healthy British women carried out by the Council of the Medical Women's Federation (1931), indicated that 62·3 per cent of those interrogated experienced hot flushes, and that headaches, vertigo and nervous instability were the symptoms which occurred next in order of frequency.

These findings merely give statistical confirmation to the symptomatology of the menopause as it has long been described in many gynaecological textbooks.

In order to compare the three groups of women who formed the subjects of this investigation, it was decided initially to make use of what Kupperman and his co-workers (1953) call the "menopausal index". This may be regarded as an expression in mathematical terms, obtained by means of a points system, of the severity of those symptoms which collectively comprise the menopausal syndrome.

The menopausal index of a woman is estimated in the following manner. The severity factor for each of a number of symptoms is individually determined. If the symptom is found to be present in a very pronounced form the maximum severity factor of three is recorded; if it occurs in moderate severity the factor will be two; and if it is present only in mild form the severity factor is represented by the figure one. If the symptom is not present the severity factor is, of course, nil.

Since the vasomotor phenomenon known as the "hot flush" is considered to be a peculiarly significant symptom of the menopause, the figure recorded for the severity factor is multiplied by a weighted factor of four, in order to give the conversion factor for that particular symptom.

Paraesthesia, insomnia and "nervousness" are considered by Kupperman and his colleagues to rank next in significance in the list of menopausal symptoms, and each of these carries a weighted factor of two. Then come mental

depression, vertigo, asthenia, arthralgia and myalgia (considered as one symptom), headaches, palpitation and formication, none of which is considered to be especially significant, so that the weighted factor for each of these is one. The sum of the conversion factors for each of her symptoms gives the menopausal index of a particular patient.

The "menopausal index" of each woman of all three groups was determined and recorded (see Tables I, II and III).

Second Investigation

The purpose of this investigation was to attempt, by means of daily temperature records, to deduce whether or not there was evidence of corpus luteum formation on the part of those ovaries which had been conserved at hysterectomy.

A multiplicity of evidence now justifies the generally accepted assumption that the elevation of temperature which has repeatedly been observed to occur in women of childbearing age, about the time of ovulation, is produced by the action of endogenous progesterone (Kleitman and Doktorsky, 1933; Kleitman, Cooperman and Mullin, 1933; Vollmann, 1940; Greulich, Morris and Black, 1943; Buxton and Atkinson, 1948; Davis and Fugo, 1948; Nieburgs and Greenblatt, 1948; Perlman, 1948; Buxton and Engle, 1950; Israel and Schneller, 1950).

For this investigation each of the subjects in Groups (*a*), (*b*) and (*c*) was instructed in the use of the clinical thermometer and asked to keep a record of her temperature for several months.

It was made clear to the subject by means of a typed sheet of instructions that the temperature ought preferably to be taken before she rose from bed in the morning, and that the thermometer should be retained in the mouth for at least three minutes (measured by clock or watch).

The necessity of taking the temperature at the same time each day was emphasized, as the basal body temperature of a woman has been shown to have a diurnal variation which is sufficiently great to obscure the diphasic pattern of the ovarian cycle if the time factor is ignored (Palmer, 1950).

The subject was instructed, on removing the thermometer from her mouth, to read it and to record the reading at once, both on a chart which was provided, and by entering the date and the figure on a sheet of paper.

The records vary in duration from one month in the case of some of the subjects of Group (*c*), to five months.

Third Investigation

The object of this investigation was to re-value the tentative conclusions of the previous investigation by the application of an additional test of their validity.

Among those temperature records not obviously monophasic there was considerable variation. The curve in some bore a recognizable resemblance to the ovulatory cycle as it has often been described in gynaecological literature, while, in other cases, the likeness was less pronounced. Where there was the suspicion of a "thermal shift" but no more than a suspicion, the record was difficult to classify and its significance remained doubtful.

It was felt that if the hint of a "thermal shift" in a woman's temperature record and the subsequent suggestion of a high temperature phase could be supported by other evidence of the production of progesterone on the part of the ovary, the probability that ovulation had occurred in that particular subject would be enhanced.

From urinary pregnanediol estimations can be derived the type of confirmation which is required, and the third investigation consisted in having the urine of the various subjects of each group estimated for pregnanediol at times selected in accordance with information supplied by the temperature records.

Although urinary pregnanediol is not the only metabolite of progesterone (de Watteville, 1951) and may indeed be the metabolite of other substances, for example, desoxycorticosterone (Cuyler, Ashley and Hamblen, 1940), yet the broad generalization that urinary pregnanediol is mainly derived from progesterone may still be considered sound.

In this investigation all three groups of women were tested.

Those whose ovaries had been removed, i.e., Group (*b*), each submitted one 48-hour sample of urine, which was submitted for pregnanediol estimation.

From the "normal" subjects, i.e., those of Group (*c*), two 48-hour samples were taken, one in the earlier part of the cycle at a time when the temperature record suggested that the "thermal shift" had not yet occurred. The second sample was taken during the latter half of the cycle irrespective of whether or not there was evidence of a significant elevation of temperature. Both were estimated quantitatively for pregnanediol.

The results obtained from each of the above groups were used as controls, the main subjects of investigation being those of Group (*a*), i.e., those subjects from whom the uterus had been removed but who still retained one or both ovaries.

From each of these women two 48-hour samples of urine were obtained and submitted for pregnanediol estimation. The object was to submit, whenever possible, one sample which had been collected during the low temperature phase of the cycle and one which had been collected during the high temperature phase. In some cases the temperature record was such that it was not difficult to differentiate the two phases, but as has already been explained, certain records did not conform very closely to the diphasic pattern. In such instances one of the samples was collected when the temperature had been elevated for a few days, though the elevation was sometimes of short duration. The other was collected when the temperature was relatively lower.

Where there was no indication whatsoever of a diphasic pattern, two 48-hour samples were collected more or less at random, but with an interval of at least two weeks between them.

The method of pregnanediol estimation adopted in this investigation was that described by de Watteville, Borth and Gsell (1948).

Fourth Investigation

The two previous investigations were designed to ascertain whether or not those ovaries which had been conserved at hysterectomy retained, after varying intervals of time, the capacity to produce the hormone progesterone.

There is, however, evidence for the belief that the concluding years of reproductive life are characterized by "irregular follicle ripening phases, prolonged transitional phases and very frequently poor luteal phases" (Bonime, 1950). Inability to demonstrate the production of progesterone does not therefore argue a complete cessation of activity on the part of the ovaries which may still be capable of producing oestrogen.

It seemed desirable, for this reason, to conduct an investigation into the state of oestrogen production in those ovaries which had been conserved at hysterectomy.

Since the action of oestrogen on the upper portion of the vaginal epithelium is essentially that of a growth hormone (Novak, 1941), promoting mitotic division of the basal cells and a resultant thickening of the epithelium, it follows that the greater the concentration of oestrogen, the greater will be the number of layers of the vaginal epithelium, the farther will the superficial cells be separated from their supplies of oxygen and nourishment and the more degenerate will they become.

The main indications of degeneration of the superficial cells are that the cytoplasm becomes acidophylic and the nucleus pyknotic. These acidophylic cells with pyknotic nuclei are said to be "cornified" and the percentage of "cornified cells" among those desquamated from the epithelium of the upper part of the vagina may be regarded as a good index of the oestrogenic activity of the ovaries (Vincent Memorial Hospital, 1950).

This investigation is therefore an attempt to discover whether or not the desquamated vaginal cells of those women whose ovaries were conserved at hysterectomy exhibit cornification, and if so, how the cell picture differs from those of the two control groups.

Vaginal smears were taken from women of all three groups. Those subjects whose ovaries had been conserved when hysterectomy was performed had smears taken daily for four weeks. Those whose ovaries had been removed together with the uterus, had smears taken on alternate days over a similar period, and from

the second control group (i.e., that consisting of "normal" women) vaginal smears were taken daily throughout one menstrual cycle.

The staining method employed was that in use at the Department of Obstetrics and Gynaecology of the University of Edinburgh and is similar to that described in *The Cytological Diagnosis of Cancer* by the staff of the Vincent Memorial Hospital (1950). The percentage of each of the three main types of epithelial cell was determined on the basis of a total count of 400 cells.

The Cells of the Vaginal Smear

A cornified cell is a large, thin polygonal cell with a clear homogeneous cytoplasm which is usually, but not necessarily, acidophylic. The criterion of cornification is thus pyknosis of the nucleus, and any superficial cell with a pyknotic nucleus has been classified as a cornified cell irrespective of the colour of its cytoplasm.

The term intermediate cell is applied to any cell of the vaginal epithelium which is obviously not a deep cell and yet does not conform to the above definition of a cornified cell.

These cells therefore vary in size and morphology, some being almost oval and possessing a relatively large vesicular nucleus, while others are thin and polygonal and bear a close resemblance to the cornified type of cell except that the nucleus is not pyknotic.

The deep cell is smaller than the intermediate cell, though larger than a polymorphonuclear leucocyte. It is somewhat rounded (or oval) in shape, the cell boundaries being precisely defined. The large centrally situated nucleus, regular in outline and containing a well differentiated network of chromatin, stains deeply with basic dyes. The ratio of the diameter of the cell to the diameter of the nucleus is about two to one.

FIFTH INVESTIGATION

This investigation is based upon the fact that the serum and urine of post-menopausal women are known to have a much greater content of pituitary gonadotrophin than is to be found in the serum and urine of the normal pre-menopausal woman. These relatively higher values are generally attributed to the progressive withdrawal of the inhibitory influence exercised by the high levels of the pre-menopausal ovarian oestrogen on the liberation of gonadotrophin by the pituitary (Bishop, 1947).

Not unexpectedly, it has also been found that bilateral oöphorectomy, when performed on pre-menopausal women, results in a similar sudden increase in urinary gonadotrophic values (Zondek, 1932).

Estimations of the pituitary gonadotrophin in the urine are conducted by the method of animal assay, and for this purpose a variety of animals have been used.

By such assays an attempt was made to obtain an indirect assessment of the oestrogenic activity of ovaries conserved at hysterectomy.

If gonadotrophic values obtained from the urine of women whose ovaries had been conserved, were significantly lower than those obtained from the urine of women from whom both uterus and ovaries had been removed, it might be concluded that, in the former group, ovarian oestrogen still continued to hold the pituitary gonadotrophin in check, and was thus an indication of the continuation of oestrogenic activity of the conserved ovary.

The male toad (*Xenopus laevis*) was employed. It possesses the advantage of measuring FSH and ICSH and may therefore be considered to reflect the potency of the subject's total gonadotrophin.

The subjects consisted of women of Groups (*a*) and (*b*). All therefore had undergone the operation of hysterectomy, some (i.e., those of Group (*a*)), having had one or both ovaries conserved, while others (those of Group (*b*)), had had them removed.

The co-operation of 20 of the 24 women (i.e., 83·3 per cent) of each of these groups was obtained.

Two 24-hour samples of urine (usually separated by an interval of one week), were obtained from each of the 40 subjects. These samples of urine were concentrated by the Kaolin method so that each ml. of the concentrate was equivalent to 12 ml. of urine (Scott, 1940).

The concentrates were assayed by the method which has been described by Hobson (1952) and also by Hobson and Landgrebe (1954).

The following is a brief account of the technique employed.

Groups of male toads (*Xenopus laevis*) were injected with concentrate and thereafter placed in separate jars. The injections were made into the dorsal lymph sac.

Four hours later, a few drops of urine were collected with a pipette from the bladder of the toad. The urine thus obtained was placed upon a slide and examined microscopically for spermatozoa, the appearance of which constitutes a positive reaction.

A clean pipette was used for each animal in order to avoid contamination. Any animal under test, which gave a negative reaction at four hours, was returned to its jar and re-examined 24 hours after injection.

The results of these assays were expressed in units of H.M.G.20A. This material was prepared by Messrs. Organon Laboratories from the urine of post-menopausal women. The groups of male toads used in this investigation were standardized against this preparation. Dose response curves were prepared and it was found that the MED50* for this powder was equivalent to 1·2 mg. of H.M.G.20A. This was called one unit.

Results

The results of the five investigations are presented in Tables I, II and III.

Discussion

Before an attempt is made to assess the probable state of the ovarian activity of each individual in Group (*a*), two considerations must be borne in mind.

In the first place, it was unfortunately not possible to investigate every subject by all the methods employed. No estimation of the pituitary gonadotrophin of the urine of subjects 17a, 22a, 23a and 24a was performed. Assessment of the ovarian activity of these women must therefore be made on the results of the four earlier tests. The remaining 20 subjects were however investigated by all five methods.

* MED50 signifies the mean effective dose which achieves a 50 per cent response.

Secondly, it must be remembered that the performance of the various tests covered a period of more than two and a half years. This means that care must be taken to ensure that what appeared to be a probability twelve months before the investigations ended, is not claimed as such a year later.

Continuation of Oestrogenic Activity

The two investigations specifically designed to supply information concerning the oestrogen-producing powers of the conserved ovaries of Group (*a*) subjects were (1) that in which the vaginal smears were examined for evidence of cornification, and (2) that in which the urine was estimated quantitatively by animal assay for pituitary gonadotrophin. It is on the results of these tests therefore that an evaluation of the oestrogenic properties of the ovaries of the various subjects must be made.

(1) *The Vaginal Smear*

Reports of attempts to classify vaginal smears according to the degree of oestrogenic activity which they are thought to exhibit, are usually somewhat unsatisfactory.

In many articles smears are described as showing "mild" or "moderate" oestrogenic activity, without the reader being made aware of the author's criteria. There is thus often a regrettable lack of precision concerning the standards by which smears have been placed in one category or another.

Anyone who has conducted an investigation on the vaginal smears of a number of apparently normal women will concede that the percentage of cornified cells to be found in the smears of one woman during a complete menstrual cycle, may differ greatly from that to be found in the smears of another apparently normal woman during a similar period of time.

The problem is made no easier by the variety of methods which have been used to measure cornification curves, and by a diversity of opinion on what constitutes a cornified cell.

To avoid a retreat into nebulous terminology an attempt has been made to express the results of the fourth investigation, as far as possible, in mathematical form, and in the hope of

TABLE I

In Which an Estimation of the Ovarian Activity of Each Subject of Group (a) is Made on the Basis of the Results of All Investigations Undertaken

No.	Menopausal Index (Age in Years in brackets)	Vasomotor Symptoms	Pattern of Temperature Record (Age in Years in brackets)	Amount of Pregnanediol in 48-hour Sample of Urine (Low Temperature Phase of Cycle, if Diphasic)	Amount of Pregnanediol in 48-hour Sample of Urine (High Temperature Phase of Cycle, if Diphasic)	Range of Percentage of Cornified Cells (Mean Values in brackets)	Results of Pituitary Gonadotrophin Estimations, Mean Values of Two 24-hour Samples of Urine (Age in Years in brackets)	Probable State of Ovarian Activity at End of All Investigations
1a	0 (40 6/12)	Nil	Diphasic (40 6/12)	0·26 mg.	14·75 mg.	7–23 (11·7)	34 units (42)	Possibly still ovulating.
2a	14 (42 8/12)	Nil	Diphasic (42 5/12)	Nil	12·75 mg.	6–40 (15·3)	26 units (43 8/12)	Possibly still ovulating.
3a	2 (48 6/12)	Nil	Monophasic (49 4/12)	Nil	Nil	4–11 (6·5)	910 units (50 6/12)	Menopause probably reached during investigations.
4a	0 (46 3/12)	Nil	Monophasic (46 9/12)	Nil	Nil	5–14 (7·2)	208 units (48 1/12)	Menopause probably reached during investigations.
5a	11 (45 10/12)	Nil	Monophasic (46 2/12)	Nil	Nil	4–11 (5·6)	399 units (48 1/12)	Menopause probably reached during investigations.
6a	1 (42 9/12)	Nil	Probably diphasic (42 9/12)	0·8 mg.	2·08 mg.	8–37 (17)	49 units (43 11/12)	Possibly still ovulating.
7a	3 (43 6/12)	Nil	Diphasic (43 6/12)	Nil	5·7 mg.	7–16 (9·1)	52 units (44 6/12)	Possibly still ovulating.
8a	2 (36 6/12)	Nil	Diphasic (36 8/12)	Nil	6·2 mg.	8–22 (10·2)	30 units (38)	Possibly still ovulating.
9a	0 (37 1/12)	Nil	Diphasic (37 1/12)	Nil	7·6 mg.	15–28 (19·1)	31 units (38 6/12)	Possibly still ovulating.
10a	12 (40 3/12)	Nil	Diphasic (40 9/12)	Nil	0·9 mg.	8–19 (9·5)	43 units (41 6/12)	Possibly still ovulating.
11a	3 (38 5/12)	Nil	Probably diphasic (39)	0·28 mg.	0·66 mg.	5–16 (8·7)	50 units (39 11/12)	Possibly still ovulating.
12a	8 (46 5/12)	Nil	Diphasic (47 3/12)	Nil	1 mg.	4–17 (7·1)	41 units (47 8/12)	Possibly still ovulating.
13a	14 (41 1/12)	Mild	Diphasic (41 1/12)	0·15 mg.	3·78 mg.	8–23 (12·4)	47 units (42 5/12)	Possibly still ovulating.
14a	4 (39 5/12)	Nil	Monophasic (39 6/12)	Nil	Nil	6–15 (7·7)	34 units (41)	Oestrogenic activity present.
15a	6 (45 1/12)	Nil	Diphasic (45 1/12)	Nil	Nil	4–14 (7·1)	23 units (46 5/12)	Oestrogenic activity present.
16a	14 (48)	Nil	Probably diphasic (48 8/12)	Nil	0·6 mg.	5–17 (8)	488 units (49 6/12)	Menopause probably reached during investigations.
17a	4 (33 2/12)	Nil	Diphasic (33 6/12)	0·15 mg.	4·2 mg.	8–17 (11·7)	Not performed	Possibly still ovulating.
18a	2 (45 8/12)	Nil	Diphasic (46)	Nil	0·65 mg.	8–20 (8·7)	54 units (47 1/12)	Possibly still ovulating.
19a	0 (46)	Nil	Diphasic (46 7/12)	Nil	0·9 mg.	4–19 (8·1)	42 units (47 1/12)	Possibly still ovulating.
20a	0 (40 4/12)	Nil	Probably diphasic (40 1/12)	Nil	0·84 mg.	8–20 (11·4)	63 units (41)	Possibly still ovulating.
21a	14 (48 4/12)	Mild	Probably diphasic (48 8/12)	Nil	3·8 mg.	4–12 (7·5)	201 units (49 8/12)	Menopause probably reached during investigations.
22a	14 (40 2/12)	Moderate	Monophasic (40 9/12)	Nil	Nil	5–29 (11·5)	Not performed	Oestrogenic activity present.
23a	4 (51)	Mild	Monophasic (51)	Nil	Nil	3– 8 (4·6)	Not performed	Probably at menopause.
24a	13 (41 3/12)	Moderate	Monophasic (41 9/12)	Nil	Nil	7–19 (8·9)	Not performed	Oestrogenic activity present.

Group average menopausal index 5·92 (S.D. 5·57).
Percentage showing vasomotor symptoms 20·83 per cent.

TABLE II

In Which the Results of all Investigations Conducted on the Subjects of Group (b) *are Presented*

No.	Menopausal Index (Age in Years in brackets)	Vasomotor Symptoms	Amount of Pregnanediol in 48-hour Sample of Urine	Range of Percentage of Cornified Cells (Mean Values in brackets)	Gonadotrophin Estimations, Mean Values of Two 24-hour Samples of Urine (Age in Years in brackets)
1b	26 (42)	Severe	Nil	Nil	309 units (43)
2b	22 (44)	Severe	Nil	1–2 (1·3)	483 units (44 11/12)
3b	17 (45 5/12)	Severe	Nil	Nil	118 units (47)
4b	12 (39 5/12)	Mild	Nil	Nil	447 units (40 10/12)
5b	36 (47 6/12)	Severe	Nil	0–2 (1·1)	200 units (48 11/12)
6b	22 (49)	Mild	Nil	0–2 (1·3)	194 units (50 1/12)
7b	26 (42)	Severe	Nil	0–2 (1·2)	264 units (43 7/12)
8b	18 (48 6/12)	Severe	Nil	0–2 (1·4)	159 units (49 10/12)
9b	2 (50 6/12)	Nil	Nil	0–1 (0·4)	219 units (51 6/12)
10b	26 (39 11/12)	Severe	Nil	Nil	187 units (41 1/12)
11b	27 (44 2/12)	Severe	Nil	Nil	420 units (45 3/12)
12b	24 (41 5/12)	Severe	Nil	0–4 (1·8)	472 units (42 6/12)
13b	27 (41 4/12)	Severe	Nil	0–2 (0·9)	275 units (43 6/12)
14b	16 (30)	Severe	Nil	Nil	552 units (31 10/12)
15b	36 (33 6/12)	Severe	Nil	Nil	441 units (35 4/12)
16b	10 (41 8/12)	Moderate	Nil	Nil	389 units (43 2/12)
17b	39 (48 1/12)	Severe	Nil	Nil	182 units (49 6/12)
18b	16 (43)	Moderate	0·25 mg.	0–2 (0·8)	287 units (44 4/12)
19b	3 (45 5/12)	Nil	Nil	0–2 (1·1)	189 units (46 5/12)
20b	4 (46 7/12)	Nil	Nil	Nil	251 units (48)
21b	4 (43 2/12)	Nil	Nil	Nil	Test not performed
22b	16 (49 8/12)	Severe	Nil	Nil	Test not performed
23b	29 (51)	Severe	Nil	Nil	Test not performed
24b	32 (46 5/12)	Severe	Nil	0–1 (0·4)	Test not performed

Group average menopausal index 20·42 (S.D. 10·41).
Percentage showing vasomotor symptoms 79·58 per cent.

TABLE III

In Which the Results of All Investigations Conducted on the Subjects of Group (c) *are Presented*

No.	Menopausal Index (Age in Years in brackets)	Vasomotor Symptoms	Pattern of Temperature Record	Histological Appearance of Endometrial Biopsy Obtained During Second Half of Menstrual Cycle	Amount of Pregnanediol in 48-hour Sample of Urine (1st Half of Menstrual Cycle)	Amount of Pregnanediol in 48-hour Sample of Urine (2nd Half of Menstrual Cycle)	Range of Percentage of Cornified Cells (with Mean Values in brackets)
1c	Nil (40 1/12)	Nil	Diphasic	No biopsy	Nil	6·3 mg.	4–18 (7)
2c	Nil (43 4/12)	Nil	Monophasic	Secretory changes	Nil	6·1 mg.	4–20 (7·8)
3c	3 (43)	Nil	Indeterminate	Secretory changes	Nil	0·9 mg.	4–17 (6·9)
4c	Nil (38 6/12)	Nil	Monophasic	Secretory changes	Nil	1·4 mg.	6–26 (11·3)
5c	4 (41 5/12)	Nil	Diphasic	Secretory changes	Nil	7·5 mg.	5–31 (9·5)
6c	Nil (40)	Nil	Diphasic	Secretory changes	0·8 mg.	2·6 mg.	4–23 (7·2)
7c	Nil (48 7/12)	Nil	Monophasic	Proliferative	Nil	Nil	3–26 (7·8)
8c	16 (49 2/12)	Nil	Monophasic	Proliferative	Nil	Nil	3–31 (10·8)
9c	Nil (39 6/12)	Nil	Monophasic	Secretory changes	Nil	5·9 mg.	6–26 (10·9)
10c	5 (42 6/12)	Mild	Monophasic	No biopsy	Nil	Nil	3– 9 (4·8)
11c	Nil (43 11/12)	Nil	Diphasic	Secretory changes	Nil	7·3 mg.	2–15 (7·3)
12c	1 (42 8/12)	Nil	Diphasic	Proliferative	Nil	1·2 mg.	2–16 (6·1)
13c	4 (42 3/12)	Nil	Diphasic	Secretory changes	Nil	7·8 mg.	3–16 (5)
14c	Nil (42 1/12)	Nil	Diphasic	No biopsy	Nil	7·5 mg.	4–30 (9·5)

Group average menopausal index 2·36 (S.D. 4·18).
Percentage showing vasomotor symptoms 7·14 per cent.

rendering discussion more lucid, the terms "cornified cell", "intermediate cell", and "deep cell" have been defined to indicate the scope of their application in the present context.

In this investigation it was also decided that the mean percentage of cornified cells exhibited in the smears of each subject over a period of four weeks should be determined, and that this figure should be used as indicative of the degree of oestrogenic activity of the ovaries of that particular woman.

This device possesses the merit of attempting to correlate the degrees of cornification shown in the smears of different subjects, on a basis that is immediately comprehensible in quantitative terms.

It was obviously desirable to relate these figures to a yardstick of normality and for this purpose a calculation was made of the mean percentage of cornified cells to be found in all the smears of all the subjects of Group (*c*), vaginal smears having been taken from this group of "normal" women daily throughout one menstrual cycle. The value obtained from this calculation was 7·9 per cent, a figure which is probably lower than might have been expected, especially when compared with some of the mean values (for percentages of cornified cells) returned by some of the subjects of Group (*a*).

It was felt that, since the mean percentage of cornified cells to be found during one menstrual cycle in the smears of 14 "normal" women was 7·9 per cent, then it was justifiable to assume that any subject of Group (*a*), whose mean percentage value for cornified cells (based on the results of 28 consecutive smears) exceeded this figure, probably possessed ovaries of oestrogenic potency equal to that of a normal woman of comparable age.

Reference to Table I will show that of the 24 women of Group (*a*) who had undergone hysterectomy with conservation of one or both ovaries, no fewer than 16 showed mean values (for percentages of cornified cells) that exceeded 7·9 per cent. It was assumed therefore that the oestrogenic activity of the ovaries of those subjects was probably equal to that of a normal woman of comparable age who had undergone neither hysterectomy nor oöphorectomy.

Moreover, since some of the normal subjects of Group (*c*) who, on the evidence of premenstrual endometrial biopsy were known to be still ovulating, returned values as low as 7 per cent (No. 1c) and 6·9 per cent (No. 3c), it is probably justifiable to credit any woman of Group (*a*) whose mean value exceeded 7 per cent with possessing oestrogenic powers which can be classified as within normal limits. By this criterion 21 of the 24 subjects of Group (*a*) may be said to exhibit, in their vaginal smears, evidence of normal oestrogenic activity.

It is interesting to observe that the remaining 3 subjects of Group (*a*) (Nos. 3a, 5a and 23a) whose mean values (for percentage of cornified cells) did not reach 7 per cent were all of an age at which the onset of the menopause might reasonably be expected to occur, their respective ages at the time of the investigation being 49 years 2 months, 46 years 10 months and 51 years.

The numbers of cornified cells found in the smears of the subjects of Groups (*a*) and (*c*) were generally lower than those obtained from comparable subjects by De Allende and Orias (1950). The difference is probably due to the fact that in the present context no cell was classified as "cornified" unless its chromatin had condensed to a solid black mass denoting pyknosis.

The similarity between the values returned by the subjects of Groups (*a*) and (*c*) is however significant, as is the contrast between these values and those returned by the subjects of Group (*b*). Among the subjects of Group (*a*) the mean percentage of cornified cells ranged from 4·6 per cent to 19·1 per cent. The range among the subjects of Group (*c*) was from 5 per cent to 11·3 per cent while the castrated subjects of Group (*b*) returned mean values ranging from zero to 1·8 per cent.

It is not within the scope of this investigation to attempt an assessment of the degree of cornification attributable to extra-ovarian sources of oestrogen. The great disparity between the degree of cornification manifest by the subjects of Groups (*a*) and (*b*) would however suggest that the conserved ovarian tissue which distinguishes the former group from the latter is the source of the significantly greater oestrogenic activity exhibited in the vaginal smears of the former group.

This investigation of vaginal smears therefore supplies no evidence that the performance of hysterectomy on a pre-menopausal woman produces a premature cessation of the oestrogenic activity of the conserved ovary.

There is moreover, considerable evidence, from the relatively high percentages of cornified cells exhibited in the smears of many of the subjects of Group (*a*), to indicate that the degree of oestrogenic activity in a woman who has undergone hysterectomy with conservation of one or both ovaries, may, two, three, or even six years later (e.g. Nos. 13a and 24a) be indistinguishable from that of a normal woman of the same age group, who has undergone no pelvic operation.

(2) *Bio-assay of the Pituitary Gonadotrophin*

Before considering the results that were obtained from the estimation of the pituitary gonadotrophin of the urine of those subjects whose ovaries were conserved at hysterectomy, it is necessary to emphasize the fact that an interval of time varying from under one year in some cases to well over two years in others, intervened between the performance of this investigation and the one that has just been discussed.

Some of the subjects who were investigated by both methods had at the time of the former test reached an age probably on the threshold of the menopause. It is not surprising, therefore, that this later investigation should suggest that there had occurred in the interim a decline in the oestrogenic activity of the ovaries, which is reflected in significantly high values for the pituitary gonadotrophin of the urines of these individuals.

Of the 24 subjects of Group (*a*), 4 (Nos. 17a, 22a, 23a and 24a) as has already been stated, did not submit samples of urine for pituitary gonadotrophin bio-assay. The oestrogenic activity of their ovaries must, therefore, be judged on the results of the fourth investigation (i.e., that concerned with vaginal smears) without the confirmatory evidence of the fifth and final test.

It was noted prior to the performance of this last investigation that, of the 20 remaining subjects, 5 reported that within the past year they had experienced vasomotor attacks. As all these women had passed the average age for the onset of the menopause in a British subject, the information was received without surprise, except for the fact that one of them (No. 21a) had previously complained of this symptom in the few weeks immediately following hysterectomy. The more recent attacks, she insisted, were, however, much more severe in character. This phenomenon will receive special comment in a later part of this discussion. The remaining 4 women had not hitherto experienced this symptom.

The values for pituitary gonadotrophin obtained from the urines of these 5 women ranged from 201 to 910 units H.M.G.20A with a mean value for this subgroup of 433·2 units.

On the other hand, the values obtained from the urines of the remaining 15 subjects of Group (*a*), all of whom were under the age of 48 years, ranged from 23 to 63 units H.M.G.20A with a mean value for the subgroup of 41·26 units.

When it is recalled that the values obtained from the hysterectomized and castrated subjects of Group (*b*) ranged from 118 to 552 units H.M.G.20A with a mean group value of 301·9 units, the significantly lower order of the values returned by these women of Group (*a*) who had not yet reached the age of 48 years, is at once obvious.

The relatively lower values which have been consistently returned by this subgroup strongly suggest that some common factor differentiates each of these 15 women both from the 5 older members of Group (*a*) and also from the subjects of Group (*b*).

By far the most probable explanation, and one that is consistent with the accepted views on the interaction of oestrogen and pituitary gonadotrophin is that the ovaries of each of these 15 women were still functioning when this test was undertaken, and that their output of oestrogen was sufficiently great to ensure that the gonadotrophin of the pituitary was maintained at relatively low values.

The results of this investigation in effect provide strong evidence that the oestrogen production of the ovaries of those 15 subjects of Group (*a*) was still at pre-menopausal level, and

that the operation of hysterectomy which each of these women had undergone at times varying from 2 years 7 months to 7 years 10 months earlier, had not abolished this form of ovarian activity.

It is noteworthy that when the vaginal smears of these 15 subjects were investigated, the value returned for the mean percentage of cornified cells found in a series of 28 smears was, in every case, within the range of values returned by the normal pre-menopausal subjects of Group (*c*).

Of the 5 subjects of Group (*a*) whose pituitary gonadotrophin values confirmed the impression that they had probably reached the menopause, 3 (Nos. 4a, 16a and 21a) had previously been classified by their vaginal smears as exhibiting evidence of oestrogenic activity comparable to that of the normal subjects of Group (*c*).

It is however necessary to add that the intervals between the two investigations were respectively 2 years 3 months, 1 year 10 months and 1 year 3 months, so that the results cannot be considered as necessarily contradicting each other.

The most probable explanation would appear to be that in the intervals, each of these subjects each entered upon a menopause which in no case could be said to be premature, and which could not logically be related to the hysterectomy which she had undergone some years earlier.

The values returned for the mean percentage of cornified cells, by the two remaining women of this subgroup (Nos. 3a and 5a) were both observed to be well below the average figure for the normal subjects of Group (*c*), so that, even when their vaginal smears were being investigated, both subjects showed evidence of a decline in the oestrogen-producing powers of their ovaries.

It is scarcely surprising, therefore, that when intervals of 16 and 27 months respectively had elapsed, they should be found to return values for pituitary gonadotrophin of the urine which strongly suggested a further decline in oestrogenic activity, a decline sufficiently pronounced to justify the assumption that both women had in the interim reached the menopause.

It may therefore be said that the results of these two investigations offer no evidence that the performance of hysterectomy with conservation of one or both ovaries produces a premature decline in the oestrogen-producing powers of the ovary.

The evidence taken as a whole would, in fact, appear to indicate that women, one or both of whose ovaries have been preserved at hysterectomy (whether it be total or subtotal in character), reach a physiological menopause at about the time when this would be expected to occur, had no operation been performed.

Continuance of Ovulation

The second and third investigations were undertaken with the object of discovering whether or not those women who had undergone hysterectomy some time previously still continued to ovulate, and it is on the results of both of these tests considered together, that a conclusion has in each case been reached.

As is indicated in Table I, 12 of the subjects of Group (*a*) were considered to have temperature records which could, without doubt be described as diphasic, while 7 were equally definitely monophasic. In the records of the remaining 5, an occasional sustained rise suggested that they also might be thought to exhibit the "thermal shift", but as the evidence was less convincing they have been designated as "probably diphasic".

The basal temperature readings of the normal subjects of Group (*c*) were, in most cases, recorded throughout one menstrual cycle only, and it is significant that in only half of these was the diphasic pattern of the ovulating subject clearly detectable.

As was to be expected, all the subjects of Group (*b*) returned temperature records which lacked any discernible rhythmic variation. In many cases the reading fluctuated within narrow limits except when an acute illness relieved the monotony of the pattern.

With these facts in mind, it is interesting to observe that when 48-hour samples of urine from each of the 24 women of Group (*b*) were estimated for pregnanediol by the de Watteville method, 23 returned zero values and that the amount of pregnanediol obtained from the urine of the remaining subject (No. 18b) was only 0·25 mg.

Forty-eight hour samples of urine obtained from the "normal" subjects of Group (*c*) during the first half of the menstrual cycle were also found, in 13 cases out of 14, to have no pregnanediol, though the sample obtained from the fourteenth subject (No. 6c) (just before the "thermal shift") was estimated to have 0·8 mg. of pregnanediol.

It is also to be noted that 48-hour samples of urine obtained from the women of Group (*a*) either at random (if the temperature record was monophasic), or during the low temperature phase (if it was diphasic), produced a similar range of results, for in only 5 instances out of a possible 24 were positive values obtained (Nos. 1a, 6a, 11a, 13a, 17a), and of these the highest was 0·8 mg.

When however one considers the results obtained from the same group of women (i.e., those of Group (*a*)) during the high temperature phase of the cycle, a totally different order of values is to be found, for in no fewer than 9 of the 24 samples the estimated content of pregnanediol exceeded 2 mg. and in 2 cases (Nos. 1a and 2a) it exceeded 10 mg.

These figures have a close affinity with those obtained from the normal subjects of Group (*c*) during the second half of the menstrual cycle for, as may be seen from a study of Table III, values exceeding 2 mg. were obtained from the 48-hour samples of urine of 8 of the 14 women of this group.

It is to be observed, therefore, that on every occasion on which other evidence indicated the absence of a corpus luteum the corresponding value obtained from the pregnanediol estimation of a 48-hour sample of urine was less than 1 mg. and in the great majority of cases was zero. The phrase "other evidence" as used here means: (1) a history of bilateral oöphorectomy, (2) the absence of a "thermal shift" in the temperature record, or (3) the absence of secretory changes in the endometria of the subjects of Group (*c*).

In those cases, however, where the temperature record suggested continued ovulation and a 48-hour sample of urine was obtained during what was thought to be the luteal phase of the cycle, values exceeding 1 mg. were frequently to be found, and in many instances, as may be observed by a glance at Tables I and III, that figure was often exceeded by several hundred per cent.

It would seem justifiable therefore to regard a diphasic temperature record supported by a pregnanediol value in excess of 2 mg. per 48-hour sample of urine (obtained during the high temperature phase of the cycle) as indicative of corpus luteum formation, and therefore as evidence of the probable continuance of ovulation.

On this basis 9 of the 24 subjects of Group (*a*) (Nos. 1a, 2a, 6a, 7a, 8a, 9a, 13a, 17a and 21a) have been classified as "probably ovulating" at the time of these investigations.

The temperature records of the "normal" subjects 3c and 4c, however, demonstrated that a 48-hour sample of urine obtained during what, on the basis of an endometrial biopsy, is assumed to be the luteal phase of the cycle, does not always produce pregnanediol values as high as 2 mg. The value for subject 3c was ·9 mg. and that for subject 4c, 1·4 mg.

This means that those subjects of Group (*a*) whose temperature records exhibited a diphasic pattern but from whom pregnanediol values under 2 mg. were obtained during the high temperature phase of the cycle may also be examples of women who, at the time of these investigations, still continued to ovulate.

These (Nos. 10a, 11a, 12a, 16a, 18a, 19a and 20a) may therefore be classified as "possibly ovulating".

Among the subjects of Group (*a*) is one (No. 15a) whose temperature record exhibited the characteristics of the ovulating subject, although no pregnanediol was obtained from a 48-hour sample of urine collected from this woman during what appeared to be the high temperature phase of the cycle.

This discrepancy may be due to the operation of some fortuitous factor producing what appeared to be a diphasic temperature record.

Alternatively, it may be that the de Watteville method of pregnanediol estimation, the sensitivity of which is admittedly limited, failed to detect a relatively small amount of pregnanediol in this particular sample.

Because of the apparent contradiction between the results of the two investigations it was

decided that the question of whether this subject was to be regarded as ovulating or not be left undecided.

Since the remaining 6 subjects of Group (*a*) (Nos. 3a, 4a, 5a, 14a, 22a and 24a) exhibited monophasic temperature records, and since two 48-hour samples of urine taken from these women returned zero values for pregnanediol, it has been concluded that these subjects were probably not ovulating when these investigations were undertaken.

Among those subjects in whom the evidence of continuing ovulation was strong, the interval of time that had elapsed since hysterectomy varied from one to six years.

Although neither the fourth nor fifth investigations which followed the ones just mentioned, were capable of giving specific information concerning the continuation or cessation of ovulation, it is significant that, of the 9 subjects considered to be ovulating on the basis of the second and third investigations, 7 were later found to return relatively low values for pituitary gonadotrophin. These later results may be said to be consistent with the earlier ones, and it is not impossible that, at the time when the fifth investigation was undertaken, ovulation may still have been occurring in some or all of these 7 subjects. That subject who forms the exception (No. 21a) had, as has already been suggested, probably reached the menopause by the time the final test was conducted. It is interesting, however, to observe that she was already 48 years of age when, by temperature record and pregnanediol estimation, she was still considered to be ovulating.

Of the 7 subjects classified as "possibly ovulating", 6 were subsequently found to return low values for pituitary gonadotrophin.

One (No. 17a) did not participate in the final investigation. The remaining subject (No. 16a) returned a high value of such degree as might be expected from a menopausal subject, when her urine was estimated for pituitary gonadotrophin eighteen months later.

It may be stated, therefore, that the study of these subjects' temperature records and the quantitative estimation of their urines for pregnanediol, together provide strong evidence that, in women who have undergone the operation of hysterectomy with partial or complete conservation of the ovaries, ovulation may continue for years, and that, since the incidence of anovular menstruation is known to become greater among women in the fifth decade (Sharman, 1955), there is no evidence on the basis of these results to indicate that the operation of hysterectomy interferes with the capacity of the conserved ovary to ovulate.

The Subjective Evidence

While an examination of the results of the first investigation reveals a general agreement with the results of those which followed it, there is good reason to maintain that symptomatology very imperfectly reflects ovarian function.

It is true that the group menopausal index of the castrated subjects (20·42) was found to be significantly higher than that of the group who had undergone hysterectomy with some degree of ovarian conservation (5·92). It should be noted however, that although subjects 2a and 13a were each found to have the relatively high menopausal index of 14, both were considered to have functioning ovaries on the basis of all four of the remaining tests.

To some extent the discrepancy is attributable to the fact that, in the determination of the menopausal index, points are allotted for symptoms that may have no association with the menopause.

Even "hot flushes", regarded by some clinicians as virtually diagnostic of the menopause, may be a faulty indicator of the state of ovarian activity.

The results of subject 13a, for example, cast considerable doubt on the reliability of vasomotor symptoms as evidence of ovarian decline, for although this woman stated, with great conviction, that she had suffered from "hot flushes" following the operation of hysterectomy, not only was her temperature record found to be recurrently diphasic, but all other objective evidence was strongly in favour of continued ovarian activity.

Not only so, but this subject (13a), on whom a subtotal hysterectomy had been performed some seven years earlier, stated that since the operation she had continued to "menstruate

regularly for about one day each month". There would appear therefore to be little, if any, reason for supposing that this woman's ovaries had ceased to function.

The experience of subject 21a also has relevance on this point. This woman stated that, almost immediately following the operation of hysterectomy, she experienced attacks of "hot flushes" which lasted for several weeks. Objective evidence obtained from the second, third and fourth investigations however suggested that her ovarian activity was far from negligible. After these tests had been conducted but before the fifth investigation was undertaken she stated that she had experienced renewed attacks of "hot flushes". Since the second attack was supported by other evidence, in the form of a high figure for pituitary gonadotrophin, it would appear reasonable to assume that the more recent phase of vasomotor symptoms did, in fact, represent the onset of the menopause, whereas her previous experience of vasomotor instability may have been no more than a transient post-operative phenomenon possibly associated with a state of general debility.

A Note on Operative Technique

Several writers have postulated a relationship between the duration of ovarian activity following hysterectomy and the technique employed by the surgeon in performing this operation. Richards (1951), for example, suggests that any procedure which puts tension on the long slender ovarian vessels may bring about thrombosis and thus destroy completely the ovarian blood supply. He therefore recommends that, after the uterus has been removed, the pelvic peritoneum should be closed without tension, so that the ovaries are left as near as possible to their normal anatomical position "in the ovarian fossa on the lateral walls of the pelvis".

Aldridge and Meredith (1950) raise a similar point when they state that the incidence of post-operative menopausal symptoms is relatively greater after the subtotal than after the total hysterectomy, a fact which they attribute to the habit most surgeons have of fixing the proximal ends of the broad and round ligaments to the vaginal vault, in order to facilitate peritonization, or as a means of support to the vagina, when performing the subtotal operation.

It is perhaps therefore worthy of mention that, at the hospital where all the subjects of these investigations underwent hysterectomy, the practice is that if the ovaries are to be conserved, the stumps of the broad and round ligaments are applied to the vaginal vault.

On the evidence of the results of these investigations the adoption of this point of surgical technique would not appear *per se* inevitably to result in loss of function on the part of ovaries that have been preserved.

It may well be however that, in the past, apparent loss of ovarian activity following hysterectomy has wrongly been attributed by certain authors to removal of the uterus, whereas the true explanation may have been that inadequate care had been taken to ensure that the blood supply is preserved.

Conclusions Reached on the Results of All Investigations

The object of these investigations was to obtain information concerning the character, degree and duration of ovarian activity in women who had, prior to the menopause, undergone the operation of total or subtotal hysterectomy with partial or complete conservation of the ovaries.

For this purpose, three groups of subject were investigated. These were:

(1) Group (*a*) consisting of 24 women who had, some time previously and prior to the menopause, undergone the operation of hysterectomy with conservation of one or both ovaries.

(2) Group (*b*) consisting of 24 women of comparable age and pelvic pathology, who had prior to the menopause, undergone the operation of hysterectomy with bilateral oöphorectomy.

(3) Group (*c*), consisting of 14 women, none of whom had yet reached the menopause, or had undergone either hysterectomy or oöphorectomy.

The investigations were five in number and consisted of:

(*a*) The determination of the menopausal index of each subject and each group of subjects.

(*b*) The examination and classification of the basal temperature record of each subject, in order to ascertain whether or not it exhibited the monophasic or the diphasic pattern.

(*c*) The estimation of the pregnanediol content of 48-hour samples of urine, collected at times selected in accordance with the pattern of the temperature record of each subject and used as a method of re-assessing the accuracy of the conclusions reached by the previous method.

(*d*) The collection and microscopical examination of a series of vaginal smears from subjects of all groups, with the object of determining the degree of oestrogenic activity (if any) manifest in these smears.

(*e*) The determination, by bio-assay, of the pituitary gonadotrophin of the urine of (1) 20 subjects who had undergone hysterectomy with conservation of one or both ovaries, and also of (2) 20 subjects who had undergone hysterectomy with bilateral oöphorectomy.

From the results of these investigations, certain conclusions emerge:

(1) Evidence obtained by vaginal smear and gonadotrophin estimation demonstrates that the oestrogenic activity of ovaries conserved at hysterectomy persists for years. There is, moreover, no indication that hysterectomy hastens the onset of the menopause. Subjects showing evidence of decline in the oestrogenic powers of the ovary were found to be of an age when the onset of the menopause was to be expected. An attempt to assess oestrogenic activity quantitatively by means of vaginal smear showed that the degree of oestrogenic potency manifest in the vaginal smears of women who had undergone hysterectomy with partial or complete ovarian conservation, was comparable to that of "normal" women of the same age group, and that this degree of oestrogenic activity might be found in hysterectomized subjects one, two, or even six years after the uterus had been removed.

(2) Evidence obtained by means of basal temperature record and pregnanediol estimation of the subjects' urine, indicated that 9 of the 24 subjects who had undergone hysterectomy with some degree of ovarian conservation might justifiably be assumed to be still ovulating at the time when these investigations were undertaken, i.e., up to seven years after hysterectomy.

Another 7 subjects of the same group also gave indication of continued ovulation, though the evidence here was less convincing.

Seven women of this group showed no evidence of continued ovulation, and the results of one subject were inconclusive.

As most of the subjects of this, the main investigation group, were over 40 years of age, and as anovular cycles tend to become more frequent as a woman approaches the menopause, it is not unreasonable to suppose that the incidence of ovulation among those women whose ovaries had been preserved at hysterectomy did not differ significantly from that obtaining in normal women.

(3) Although symptoms usually associated with the menopause were found to be more prevalent among the castrated subjects than among those who had undergone hysterectomy with conservation of one or both ovaries, such symptoms were found to be an unreliable indicator of the state of the ovarian activity of the individual.

(4) It is suggested that the apparent loss of ovarian activity which some writers have reported as following hysterectomy, may have arisen from failure to ensure that the conserved ovary is left with an adequate blood supply. Ovarian atrophy and loss of function is not, however, likely to be a necessary consequence of applying the stumps of the round and broad ligaments to the vaginal vault, since this practice is followed at the hospital in which the subjects of these investigations underwent hysterectomy. As the foregoing pages of this article indicate, continued ovarian activity is manifest in the majority of these subjects years after operation.

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REMINISCENCES OF FIFTY YEARS MEDICAL PRACTICE, FORTY-SEVEN OF THEM SPENT IN SOUTH AFRICA*

BY

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MR. Chairman, Ladies and Gentlemen. When our good friend, and late President, Sir Charles Read invited me to give the William Meredith Fletcher Shaw Memorial Lecture, my first reaction when I read his letter was "What a great honour he is conferring on me!" I had a feeling of pride. Immediately following this came a sinking feeling for I felt I was not capable of giving a lecture which would compare at all favourably with those given by so many eminent men during the last 10 years. I felt very diffident about giving it but also felt that I must do what I could because of the very high regard in which I hold Sir William Fletcher Shaw who I understand instituted this lectureship in memory of his son who sacrificed his life for his country during the last war. Some of us who had sons taking part in that war were more fortunate than Sir William for we still have them alive with us today and our sympathy goes out to him with all the greater sincerity for we realize how much he has missed.

My next thought was "What in all the world can I talk about?" I harbour no illusions about myself and am quite aware that there is no obstetrical or gynaecological subject of which I have made a special study and about which I could speak with greater authority than anyone else. I have, however, out of my 50 years of active medical practice, spent 47 of them in South Africa, and during that time seen developments take place from the most primitive conditions to the most modern conditions, so hope I may be able to impart some information to you regarding changes that have taken place in South Africa during nearly half a century and be able to interest you for a short time. I have therefore called my lecture "Reminiscences of 50 years Medical Practice, 47 of them spent in South Africa". These reminiscences will be a kind of pot pourri in which some of the rose petals of memory have been brought to the top; they will be rambling remarks and comments about some of the changes which I have seen take place since I was a student.

I cannot refrain however from recounting to you my first practical experience of midwifery —my first attendance at a confinement. Well do I remember it. Late in the afternoon of Hogmanay, the last day of the year 1906, I arrived at the Livingstone Memorial Dispensary in the slums of Edinburgh where I was to reside for the next 6 months.

I was busy unpacking when a fellow student called Peake, a New Zealander, barged into my room and told me I must hurry and go at once to a confinement. I was dumbfounded and scared stiff at the thought. There were usually 12 students resident and a qualified Superintendent. The latter was out at one confinement, Peake was busy with another and I was the only other student available for it was holiday time. But please note:—Not only had I never seen a case delivered for I had not been inside a maternity hospital, but I had not even had lectures on normal labour and here this poor woman was to be entrusted to my tender mercies.

I protested strongly but was told I must go as there was no one else. Metaphorically speaking, I almost went on my knees to implore Peake to

* The William Meredith Fletcher Shaw Memorial Lecture delivered at the Royal College of Obstetricians and Gynaecologists on 25th July, 1958.

come to my assistance as soon as his own case was delivered. I looked upon him almost as an expert for in the few days he had been there he had delivered 3 cases!

So out I went and had a very sudden introduction into the seamy side of life in the slums —filth, drunkenness, utter depravity and poverty, all seemingly made worse in those days by the women wearing shawls and skirts so long that they swept the filthy muddy streets. That was the fashion and of course had to be followed even in the slums. As Jerome K. Jerome said "Women were not supposed to have legs in those days".

I trudged along the Grassmarket to the West Bow, mounted the steps and entered, in fear and trembling, a room, not so filthy as I expected, to find a girl of 19 having her first baby. Some kind woman (and I found there was much kindness of heart and sympathy among the poor) had taken this poor girl in in her extremity, for her parents had turned her out of house and home because of her apparently unforgivable sin of having become pregnant outside of wedlock. (At that time Dr. Loomis had not published his book *Consulting Room* in which he remarks that "one of a gynaecologist's chief functions is to assist the human female how to correlate her biological instincts with the dictates of Christian Ethics".)

I was terrified when, with each contraction, I saw something bulging the perineum and later saw a head with dark hair protruding; fortunately it receded each time. How long that head remained there I do not know. It seemed hours but certainly it was much longer than students are *now* taught to leave it there. But I prayed hard that it would remain there till the specialist, my student colleague, arrived, and at long last he did. My troubles were over. Mother and baby did well "Thanks to the doctors".

I had attended my first confinement and had learned on my own, something which was drilled into me later—the importance in many cases of masterly inactivity. When I think of this experience I am always reminded of a Cartoon in the Edinburgh University Magazine of my day—"The Student". It depicted a heavy coarse looking muscular woman standing at her door, arms akimbo, looking scornfully down at a scared, bespectacled, diminutive student with his bowler hat on his head and his midwifery bag in his hand. Underneath the drawing were the words "Did you send to the Dispensary, Madam?" and "Yes, my boy, for a Doctor".

I have detailed this experience to show the younger members of my audience that in my undergraduate days it was not necessary to enter a maternity hospital. All my training was done "on the District" and these cases were usually conducted by myself; sometimes two students went together and occasionally a Queen Alexandra Nurse was present. We sent for the Superintendent only if we considered there was some complication. It was certainly an excellent training for it developed a sense of responsibility. I remember delivering twins, a breech, having a case of eclampsia (there were no antenatal clinics then) and applying forceps while the Superintendent administered the anaesthetic. Needless to say I have grave doubts *now* as to whether such practice was in the best interest of the patients.

In passing let me say that similar responsibility devolved upon us in connexion with all medical and surgical cases which required domiciliary attention. We really acted like qualified medical men and only called in the Superintendent when we were puzzled about the diagnosis or the patient seemed very ill. Further may I add that when I went into general practice, I found this dispensary experience more valuable than any of my other clinical training.

I visited this Dispensary in 1954. For some time before this it appeared that its days of usefulness were passed but I found to my great satisfaction that the National Health Service had taken it over and it appeared to play an important part in the teaching of general practice to students again.

During my last year as a student, I had to borrow money to finish my course. For the same reason I found it impossible to think of applying for a post in the Edinburgh Royal Infirmary. Instead, I accepted a post as assistant to a man who proved to be an excellent general practitioner, Dr. Crerar of Maryport. I was with him for two years and the experience I gained was most valuable. In South Africa one of the rules

laid down before a candidate can be admitted to the specialist register is that he must have spent two years in general practice—an excellent provision in very many ways and especially if he could spend it under the tutelage of a general practitioner such as Dr. Crerar. (In passing let me say that this rule has been modified to a certain extent.) It may interest some of you to know that my salary was £150 a year living in and practically all the visiting was done on foot or on a bicycle.

Having liquidated my debt by this time I returned to hospital work for a year at a salary of £100 a year. Now general practice seemed to be my destined career and I began to look around to see where I could settle in Britain but sometimes, at any rate, Shakespeare's words seem true. "There is a divinity that shapes our ends rough-hew them how we will." One can hardly call Lloyd George a Divinity but perhaps he was the instrument used! At any rate this year 1911 was the year in which the first step was taken towards the National Health Service you have now, for it was then that Lloyd George brought in his National Health Insurance Scheme. Wherever I went or enquired I was advised not to think of a practice then for everyone seemed to think many practices were going to be ruined. As the prospect seemed grim and as I had become engaged to my boyhood sweetheart, I was determined to go abroad and try my fortune in Canada. I had written to a fellow student who had settled in Vancouver and he advised me to come out.

In those days, and I think the same conditions prevail there today, it was essential to pass all four professional examinations again and I started studying Chemistry, Physics, Botany and Zoology.

I have included what follows on the advice of Professor Louw of Cape Town. One evening in November last he asked me what decided me to come to South Africa. I recounted the details to him and he said "Oh, you must include that in your lecture".

It would almost seem that Fate stepped in again. By August, 1911, I had booked my passage for Canada for a certain Saturday in the middle of the month. I had arranged to spend the weekend previous to my sailing with my relatives and friends in the village in Fifeshire where I was born and brought up. Those of you who knew Edinburgh in those days will remember the old slow cable cars. I was travelling in one towards Waverley station and as it was raining I had to sit on the edge of the back of a seat on the upper open deck. As a car approached from the other direction I spotted a student friend, Frank Jardine, who many years later became President of the Royal College of Surgeons of Edinburgh, and he spotted me. He just had time to shout "You must come and see me". That chance encounter is responsible for my being a South African today instead of a Canadian.

I saw him on the Monday when he told me that Professor Caird wanted to see me regarding an assistantship in South Africa. I saw him in the Royal Infirmary and he told me the post was worth £400 a year but he could not say whether I would be living in or out. This of course meant a very big difference, for living on the Witwatersrand in those days was reputed to be twice as expensive as in Britain—a contrast from the present day. It was decided to cable out to the Dr. Macaulay who was endeavouring to find the assistant for a Dr. Grace. Remember this was Monday and I was due to sail on Saturday. I anxiously waited for the reply but Tuesday and Wednesday passed and then on Thursday the cable was returned. It had not been delivered and I found out afterwards that Dr. Macaulay's cable address printed on his paper had not been paid for that year! Another cable was sent on Thursday morning to his full address.

Meanwhile I saw another old friend, Dr. E. B. Jamieson, the anatomist, who had heard I wanted to go abroad. He informed me that he had a request for two assistantships in the Cape Province. This looked as if I were meant to go to South Africa and as there were no examinations to pass and as I would have some definite post to go to, I decided to cancel my passage to Canada. This was done on Friday afternoon, some 16 hours before the ship was due to sail. The answer to my cable came a few hours after the ship had sailed and this was its wording. "400 living in must be Scotsman."

I sailed for South Africa two weeks later on the 2nd September, 1911 and was surprised to

see at Waterloo Station, Dr. Jolly, who had been my lecturer in Chemical Physiology at Edinburgh, dressed in frock coat and tile hat, appropriate attire I presume, for he was proceeding to Cape Town as the first Professor in Physiology in South Africa. Fortunately, in my new contract, there was no stipulation that I must wear such attire though it was insisted upon for a fellow student who had gone as an assistant to Port Elizabeth a short time before. In fact *I* made myself conspicuous by wearing a bowler hat the day I arrived at my destination and that same afternoon I discarded it and have not worn one since.

My destination was Springs, a town on the East Rand, 30 miles from Johannesburg. It was a small town of a few hundred inhabitants and there was no electric light and no water-borne sewerage. It had depended chiefly on a few small coal mines but was destined to become the centre of one of the biggest gold producing areas, and today it is the 10th biggest town in the Union with a population of about 131,000. Remember that in 1911 Johannesburg was only 26 years old. My chief, a Dr. Gerald Grace, was a nephew of the famous Dr. W. G. Grace, the cricketer.

My first week in Springs was a most depressing one and had I been a man of means, I think it is quite possible I would have taken the first ship back to the old country, but I had borrowed money for my passage, so I had to accept conditions as they were.

The practice was a varied one. Dr. Grace had contracts with three of the gold mines to look after the health and housing of the native employees. There was only one mine producing at that stage and two were at the stage of sinking shafts to the reef, some 4,000 feet down. He was also medical officer to the native employees on two small coal mines and attended to the European employees on these 5 mines through Benefit Societies; there was also a moderate-sized private practice among people in the town and amongst farmers, storekeepers and others in the surrounding country. There were then two other medical practitioners in the town, one of whom became famous in a different sphere in later years and had many honours thrust upon him by various scientific societies—Dr. Robert Broom the Palaeontologist.

The condition of the natives on the mines was very distressing to one unaccustomed to their prevailing living conditions. They were all housed in compounds and the cleanliness of their quarters was certainly not all that could be desired. But their feeding was deplorable. There was no balanced diet; the chief constituent was Mealie Meal (maize) with some meat once or twice a week. It was not to be wondered at that diseases of all kinds were rampant and it was not uncommon to find 10 per cent of the employees in hospital either with diseases or accidents. Tuberculosis of the lungs and of the abdomen was very common and pneumonia was rife; pneumococcal pericarditis was common. In those days it must be remembered that the death rate from pneumonia was about 33⅓ per cent.

One disease puzzled me at first as I had not encountered it before and my chief evidently had not diagnosed it. It manifested itself by big brawny painful calves and great weakness. It caused any number of deaths and post-mortems revealed ante-mortem clots in the heart and dark blood infiltrating the muscles. It proved to be scurvy though the manifestations in the gums were not very marked—the sign I remember being taught as pathognomonic. An interesting point discovered was that most of these cases developed the disease a few weeks after starting work on the mines. We knew nothing of vitamins in those days but I think there is little doubt that the natives in the kraals as long as they were not working (for in their territories they did little work while their women folk cultivated the lands) consumed sufficient vitamins to keep them fit, but not sufficient when they performed hard manual work.

A treatment which was instituted by a Dr. Donaldson of Crown Mines may interest you, viz., the intravenous injection of orange juice. The oranges were left in a solution of carbolic for some hours. They were then washed in sterile saline, cut up with sterile scalpels, the orange juice squeezed out through sterile gauze and, after being neutralized, the fluid was injected. I cannot tell you how many of these intravenous injections I administered. They were certainly of great help but it was soon found out that it was just as effectual, much

pleasanter for the patient and much less trouble for the doctor to administer the fresh oranges orally.

The native hospitals however were what disturbed and distressed me most. They were so overcrowded that in some the wooden beds were placed up against each other and often one had to walk over the patients to be able to get at them. The beds were about 15 to 18 inches high and consisted of wooden slats across them. My first proper inspection of these beds and the 1 inch thick piece of felt which formed the only mattress revealed and disturbed a mass of insect life which I had not imagined possible. A special bath was made afterwards in which these beds were boiled regularly.

The nursing was done by white men called hospital orderlies and by native attendants. Neither of these classes had any real nursing training but apparently had just picked up some elements of nursing in haphazard ways. You can imagine the absolute dread of having to do any operations under such circumstances and yet it is marvellous what operations were done and how well most of the patients recovered. Most operations performed were for accident cases which of course were numerous. I cannot attempt to describe the conditions any further; it would take too long.

I am sure you must all wonder why the medical officers of the mines allowed such appalling conditions to persist. Well I soon discovered that at most medical meetings this state of affairs was ventilated and that recommendations were made to the mining authorities who appeared to take little notice of them. They could not be made to realize that it would pay them to have a well fed, well housed, healthy labour force. I have often in my own mind compared the conditions with the conditions that prevailed during the time of the Industrial Revolution in Britain at the end of the 18th and the beginning of the 19th century. The conditions however were much worse because the native labourers were a primitive people of no education at all, drawn from numerous tribes from the native territorities, speaking numerous unwritten languages and with various religious or irreligious beliefs.

But, as Bryant mentions in his "English Saga", such conditions ultimately arouse the conscience of a people as a whole and in 1912 the Government of the day insisted upon an investigation and Colonel Gorgas of Panama Canal fame was brought to South Africa in 1913 to investigate and report on the whole situation. His report was an illuminating one and it largely endorsed the expressed opinions of the medical men working on the mines. Government regulations were brought into force regarding housing, feeding, etc., and it may be said that ever since that time conditions have steadily and regularly improved. The Mining Authorities were ultimately convinced by results that it paid them to look after their native labourers well. Now the mines have full-time medical officers and can be proud of the conditions which prevail. Most natives are migrant labourers who come to the mines for periods of 6 to 12 months. They are medically examined by medical officers before they leave the territories, again at a central depot in Johannesburg or elsewhere and again at the mine to which they have been allotted. One of these examinations includes an X-ray of the chest, mass miniature radiography being employed; this means the taking of some hundreds of thousands of X-ray photographs each year for periodical X-ray examinations are also made during their term of employment and at the termination of the contract. These are compulsory, laid down by an act of Parliament of 1956. When they return to their homes in their territories most of them go back in a much better physical condition than when they arrived. I fancy there are few industries anywhere where employees are better cared for. I visited recently one of the new hospitals at Welkom built by the Anglo-American Corporation for several of its new gold mines in the Orange Free State. I can assure you you would be amazed at this 900 bedded modern, up-to-date native hospital equipped with everything of the latest, including an artificial kidney unit.

Do remember when you hear hard criticisms of the conditions under which South African natives work and live that there is much to be said on the credit side also.

Now I must say something about general practice. At first I was provided with an ordinary

cycle and a horse and trap and I thought nothing of cycling or riding 6 miles to the mines and back again, but after about two months I was given a motor cycle and many thousands of miles I must have covered on Triumphs, B.S.A.s, etc. There were no tarred roads in those days. The roads were chiefly veld roads, just hardened tracks through the country though the road to Johannesburg was always passable; this was fortunate for the nearest Provincial Hospital for Europeans and Non-Europeans was at Boksburg, 15 miles away, half way to Johannesburg. Our European Accident and Sick cases were attended there. This involved daily visits or visits every second day but I remember well paying three visits on my motor cycle on one day and having to do a cholecystostomy for an empyema of the gall bladder on my third visit.

Visits to the country districts however were the ones which were looked forward to with some trepidation for one never knew what the roads would be like and whether they would be impassable on the return journey if a sudden thunderstorm developed. Also one never knew whether one was going to meet with some very simple condition or some serious emergency 50 miles away from any help and please note that there were often no telephones, no ambulances and hardly any cars.

It may interest you, if there is time, to describe some of the obstetrical emergencies I met with. I remember well one of my early cases, some 25 to 30 miles in the country. All one could get in the way of information from the native messenger was that the native woman had been in labour for about two days and the baby would not come. I asked my chief what I should take with me and he told me to take my ordinary midwifery bag saying "It will be all over by the time you get there". So off I went on my motor cycle with the bag strapped on the carrier behind. I was directed how to go so far and there I was met by a native with a Cape cart and two horses. I followed him for a few miles but ultimately there was no road and it was impossible to take my motor cycle further. There were no self-starters in those days. One had to run alongside the motor cycle for a few yards each time to start the engine. I transferred to the Cape cart while the native pushed my cycle the remainder of the way. The ride in the Cape cart guiding two unknown horses over the veld, avoiding pot holes and large ant heaps, was certainly an adventure for me but I arrived safely.

Then my troubles began! I was shown into a native hut, lit only by the light from the door and from what we in Scotland used to call a bole in the wall, a small square opening closed with a wooden shutter, and opened when light was wanted.

On one side of the hut were bags of mealies and lying on the earthern and cow dung floor was a native woman with a projecting foetal arm seen at the vulva and a uterus in tonic contraction. It is wonderful what these natives can stand. I had then to decide what was to be done. Fortunately it was daylight and therefore I was able to get some light from the bole in the wall. The water from a hole in the ground was brown with mud but I managed to get some of it boiled and much Lysol (*the* antiseptic used in those days) was added to the water in two basins which I had scoured out with pure lysol. What instruments I had were rubbed with pure lysol and put in the basin. About the only instrument of any use was a pair of 6-inch surgical scissors which I always carried in my waistcoat pocket.

Then I managed to secure a big box about 2½ feet high on which the patient was placed in the lithotomy position and one raw native woman held the one leg in position and another held the other one. Then I proceeded to anaesthetize the patient with chloroform and, after she seemed sufficiently under, the open Schimmelbush mask was handed over to a third raw native and, while I washed up and during the delivery, I kept nodding my head when I wanted a few more drops added. (Remember I knew none of their language.) Then I proceeded to perform my first decapitation, the first one I had seen, with my pair of 6-inch scissors. Version was impossible for I could not ask the anaesthetist! to put the patient deeply under. But by pulling on the arm and getting my left forefinger just above the neck, I managed ultimately to cut through the neck with these scissors and succeeded in getting the body away.

Luckily I had no difficulty in extracting the head. On inspection of the vulva after that, however, I was distressed to see numerous small wounds around the urethral opening. Evidently while I had been using the scissors I must have been pressing up against the lower border of the pubes using it as a fulcrum. I had visions of having to return next day to pass a catheter but I heard nothing more so she must have done all right. I remember my financial reward for all this was £5, procured after the husband had sold an ox, but I gained much more in experience and confidence in myself, I had learnt also to be equipped to tackle maternity emergencies.

Soon afterwards I had a case with which I was not as fortunate. One evening a message came by the railway telegraph to come to a farm house 48 miles away. In the darkness of the veld it would have been impossible for me to have found my way so it was arranged that I take my motor cycle and myself in the guard's van of a goods train to Leslie, 40 miles away. (Curiously enough this village or dorp "Leslie" was named after the Scottish town in which I was born.) The other 8 miles was done in a Cape cart driven by the European farmer. It was made memorable to me by the fact that dogs running alongside the cart encountered and fought a muishond or skunk and I can assure you that that animal's defence mechanism in the form of an appalling disgusting odour is a most effective one. The dogs carried the smell all the way to the farm house.

Arrived there I found a European woman nearly pulseless lying in a blood soaked bed; a dead baby had been born. I had learnt by this time to carry a needle and tubing and glass funnel with me and proceeded to prepare a normal saline solution, boiling it on the kitchen stove. There were no prepared vacolitres in those days—in fact no intravenous injections were even thought of and I introduced my prepared normal saline solution into the submammary region but it all availed nothing and the patient died about an hour and a half after my arrival.

I was driven back to Leslie station and set off on my 40 mile motor cycle ride back to Springs. I have not forgotten that ride either for I had about 7 punctures on the road and as there were no spare wheels carried in those days I had to sit down in a broiling sun and mend each one. I started at 8 a.m. and reached home at 4 p.m.—dead beat. I went to bed and slept till next morning.

In 1913 two events of importance took place. I was taken into partnership by Dr. Grace and I entered into the greatest and happiest partnership of my life by marrying the girl I left behind me in Scotland and to whose inspiration what little success I may have achieved in life is largely due—a tribute which now I am very pleased publicly to express to her memory.

A few months after her arrival I well remember a call to the country one afternoon. My wife and I and a friend had arranged to take the train into Johannesburg that afternoon to dine there and go to the theatre. They went on their own and I went to this maternity case on my motor cycle. I arrived to find a European farmer's wife and twins all dead and no one but a native woman in the house. What happened to the husband, I never knew.

I rushed back to Springs and caught the next train to Johannesburg, and enjoyed the theatre. We reached home about 1 a.m. to find one of the doctors in town waiting for me and I had to proceed to another confinement.

In August, 1913, I acquired a motor car. I wish you could see it now. My income for that year was £507 so naturally I could not afford a new car. It was a make one never hears of nowadays—a Calthorpe—and it cost me £80, a two seater with two acetylene lamps and two side paraffin lamps. It had no windscreen at all but had a cover which one pulled forward and attached with straps to the front mudguards but if it rained heavily or there was a dust storm one usually turned it round to let the rain or dust strike it from the rear and waited till the storm passed. I think I knew every little bit of that car and I cannot say how often I had the carburettor to pieces. Still in many ways we found it a great joy and I was able to have my wife's company on those country trips.

Let me describe one of the early trips. By this time the telephone had been installed in some of the villages around. One evening a telephone message from a village 18 miles away was received to come to visit a European woman who

was "suffering badly from asthma", and would I "please bring out medicine with me for it". I got to the village and found I had to go to a farm seven miles farther on.

On entering the bedroom I found any number of relatives and friends there; that usually implied in a Dutch house that the patient was very ill or dying. I now saw this was no case of asthma. The patient over 40 years of age was sitting up in bed. She was very cyanosed and she was about 8-months pregnant. One had only to look at her to realize that she had a laryngeal obstruction. She was so bad that I could not get a look at her throat but I concluded she must have diphtheria and it was evident she needed a tracheotomy. I cogitated for a little while wondering what to do; it seemed impossible to drive her into hospital 40 miles away and I felt it would be impossible to get any doctor out 25 miles with instruments, anaesthetics, etc. I found out from the chemist who had accompanied me from the village that he had no chloroform or ether as he was never asked for them.

Suddenly Providence or fate, call it what you will, ended my cogitations for the patient fell back on the bed apparently dead, many of the relatives leaving the room crying and saying "Sy is dood, Sy is dood". I turned to the husband and said "There is only one chance, will you let me open her windpipe"? He immediately consented and I took from my waistcoat pocket the small instrument case which I always carried with me. It contained a thin scalpel and a bistoury which folded together, one tiny artery forceps, a dissecting forceps, probe and director, none of them 3 inches long. I pulled the woman across the bed with her head hanging well down and steadied it between my knees. Then I simply stabbed through the trachea in the midline and incised the first two or three rings. There was no attempt at dissection. The handle of a teaspoon was pushed into the trachea and turned at right angles to keep the trachea open. In her cyanosed condition she bled a good deal but this I am sure was most beneficial. Then I directed the husband on one side and a grown-up son on the other to do artificial respiration, each using one arm. To my intense satisfaction and rather to my amazement she gave a gasp after a little while. I cannot pretend to say what time had elapsed but eventually regular breathing was established. Up till now, no antiseptic had been used and all I could find was on a little bedside table—an antiseptic more commonly used internally than externally, another excellent product from Scotland—Scotch Whisky. I had of course no tracheotomy tube but a piece of my stethoscope tubing acted well as a substitute and with a safety pin and tape round the neck, the operation was completed. I could not stay all night and showed the husband how to keep the stethoscope tubing clear by using a hen's feather. Next morning she was brought twenty-five miles to my house in an open car and after I had attended to her, she then completed the next 15 miles to Boksburg Hospital. Bacteriological investigation proved the offending organism to be a Streptococcus and the standard treatment of those days was given—anti-streptococcal serum. Ordinary wound treatment was given and the wound closed excellently. She was out of hospital in less than 3 weeks and I am glad to say that 4 weeks from the time of the tracheotomy she gave birth to a healthy living child. It is hard to imagine such a combination of fortunate circumstances but I think that case gave me then, and has given me since, more satisfaction than any other case I have ever attended. To a young man, it also brought great kudos and months after I remember being called to another farm house in a different direction and being asked (in Afrikaans) "Are you the doctor that brought Mrs. E. back from the dead?"

I may add that I cannot remember the fee that was paid though I think it was about £15, but I remember the husband unlocking a chest, pulling out a canvas bag and paying me out in golden sovereigns.

I must now skip a few years. I was in the Persian Gulf the day peace was declared in 1918 and I spent about 6 months in Mesopotamia (now Iraq) after that. I was in the R.A.M.C. This, I think was the laziest six months of my life and it was during that time that I made up my mind to endeavour to specialize in Obstetrics and Gynaecology—an ambition which I had always cherished though I had seen little chance

of achieving. After I returned to Springs in August, 1919, I hoped I would be able to proceed to Britain in about 3 years time to carry out this plan. Alas, many vicissitudes contributed to postpone my departure and it was not until 1927 that I felt able to burn my old boats and embark on this new venture.

I spent nearly 2 years in Britain, most of the time in Glasgow and I cannot speak too highly of the great help and hospitality I received from numerous colleagues. I cannot refrain, however, from paying a special tribute to the late Professor James Hendry to whom I owe so much; but for his help and advice I do not know how I would have gained the necessary experience. A student friend of his, whom I had taken into partnership, had promised to write him to introduce me, asking him also to do what he could for me. Not till I was leaving Glasgow about two years later did Hendry inform me that this mutual friend had never written him. Truly "I was a stranger and he took me in". His early death was a great loss to our speciality.

To his assistant at that time, Dugald Baird, now Professor at Aberdeen, I also owe a debt of gratitude for his great help and kindness. We have been friends ever since. It was in 1927 in Manchester that I met Sir William Fletcher Shaw for the first time and experienced his charm and kindness. Now I feel proud to call him friend.

I had planned to visit Dublin and Vienna but these visits had to be cancelled because a colleague in Johannesburg died suddenly and Professor Gordan Grant, to whom I also owe a great deal, advised me to return to Johannesburg at once. Through his good offices (and I hope to some extent on merit) I was appointed to the staff of two hospitals and to that of the Medical School.

Never in my wildest dreams did I imagine that in ten years I would succeed Professor Grant in the Chair of Obstetrics and Gynaecology at the University of the Witwatersrand. I think it is highly probable that I may be the last Professor in our speciality to have spent over 20 years in general practice prior to appointment.

Time will not permit more personal reminiscences but I would like to draw your attention to some of the wonderful developments which have taken place in the South African Medical World in the last 47 years and of which many of you must be unaware.

When I went to South Africa, Johannesburg was only 26 years old at that time, 1911; it had a population of 237,220. Now it has a population of over a million, nearly half of whom are Whites. South Africa had no Medical Schools then and each of the four provinces had its own Medical Register.

The University of Cape Town was the first to start a Medical Faculty though in 1905 the British Council of Medical Education gave full recognition to the 1st year Medical Course in the South African College. You will remember I stated that the first Professor of Physiology, Dr. Jolly, and I voyaged out together on our first trip in 1911. Dr. Thomson, also of Edinburgh, became the first Professor of Anatomy. Classes started in 1912 but only for 2nd year of Medicine. Students had then to proceed to Britain or elsewhere to complete the remaining three years. The first world war broke out in 1914 and it was not till 1919 that Clinical Professors were appointed. The full course was initiated in 1920 and the first students graduated at the end of 1922—2 in number. The first Professor of Obstetrics was Dr. E. C. Crichton who retired only a few years ago. A Foundation Fellow of the College, he was, for many years Chairman of the South African Reference Committee of our College and is still a member of the South African Regional Council which has now been in existence for 2 years.

Since its first graduation 35 years ago, the University has conferred qualifying Degrees on 2,701 individuals, an average of 77 per year. The largest number in any 1 year, a few years after the last war, was 184. The first Non-Europeans were admitted to the Medical School about 1939. I cannot say how many have graduated since then.

The Medical School of the University of the Witwatersrand was inaugurated in 1919 and the first graduation took place in 1925 when there were 4 graduates. Since then 2,648 have graduated, the largest number in any one year being in 1952 when 178 graduated.

The first Non-European qualified in 1941 and since then 161 have qualified. The total number of M.B., Ch.B., students at the University this year is 577. At first there was a Professor of Obstetrics, Dr. McGibbon, and a Professor of Gynaecology, Dr. Gordon Grant, but, when Professor McGibbon was appointed to the Chair in Dundee, Professor Gordon Grant was appointed to a Chair of Obstetrics and Gynaecology. A Foundation Fellow of the College and a former member of the Reference Committee in South Africa, I am glad to say he is still enjoying a retirement in Natal.

Next to inaugurate a Medical School was Pretoria University. It commenced in 1943 and 44 students graduated in 1947. The largest number to graduate in any one year was 109 in 1949 and since its beginning 824 have graduated. The Pretoria University does not train any Non-Europeans. Professor te Groen, also a Fellow of the College, was the first Professor of Obstetrics and Gynaecology and has also been a member of the South African Regional Council. He also has retired but I regret to say he is not enjoying good health at present.

The University of Natal was next to start a Medical School. While certain provisions exist regarding the possibility of Europeans being admitted, it can be said that the present South African Government, in conformity with its policy of Apartheid intends this Medical School to remain, as it is at present, one for Non-Europeans only. I cannot enter into more recent developments which at present are causing much disputation and controversy. The first group of students entered this faculty in 1951 and the first 12 students qualified at the end of 1957. The course is really a 7 years one as the Faculty from the first introduced an extra preliminary year. As the Dean expressed it to me, "Our University feels strongly that the particular course of training which we follow is in many respects more in accordance with Curricula overseas, more particularly in the United States of America and on the Continent". Personally I think this extra training is probably more necessary for the Non-European students as many of them lack the background associated with Western Culture and tradition.

The students at present comprise Africans, Indians and Coloureds of both sexes. The African students are of all cultural and tribal groups from the 4 Provinces of South Africa, from the Central African Federation and from the Basutoland Protectorate. The total number of Non-European students in the 7 years now is 197. Dr. E. D. Crichton, son of Professor E. C. Crichton of Cape Town, was the first Professor of Obstetrics and Gynaecology.

Stellenbosch University is the most recent one to inaugurate a Medical School and at present it has reached its 3rd year of training with 65 students in its 1st year, 52 in its 2nd year and 29 in its 3rd year. There is every likelihood of an increase in these numbers. Stellenbosch University also has no Non-European students. Dr. J. V. de Villiers, M.R.C.O.G., is the recently appointed Professor of Obstetrics and Gynaecology. I am glad to say that all the past and present Professors of Obstetrics and Gynaecology have been or are Fellows or Members of our College.

I am sorry I cannot give you the number of Medical Practitioners on the Registers of the 4 different Provinces in 1911. The earliest I have is that at the end of 1932 when there were 2,442. At the end of December, 1957, i.e., 25 years later, there were 7,352—nearly 5,000 more. This will give you some idea of the development that has taken place.

Even more striking is the fact that there were hardly any specialists in South Africa in 1911. I have already mentioned that there were only 3 in Johannesburg, one being an Obstetrician and Gynaecologist, Dr. Gordon Grant, and I think there was not another one in South Africa then. Yet at the end of December last year there were 1,370 registered specialists in the Union and 126 of these were Obstetricians and Gynaecologists.

In 1911 most of the doctors had graduated in Britain, a large proportion of them in Scotland. Note the contrast at the end of December, 1957—70·23 per cent of the 7,352 on the register had graduated in South Africa, 13·02 per cent in England, 11·75 per cent in Scotland and 3·66 per cent in Ireland.

Never shall we forget how much we owe to British Medicine in the past and how much it has contributed to the present position of South

African Medicine. You have thrown open wide your Medical Schools and Hospitals to train our undergraduates and postgraduates and your hospitality has been unbounded.

I regret, Mr. Chairman, that I have been able to give you only a fragmentary account of the medical developments which have taken place in South Africa in the last 47 years but I hope the pictures I have attempted to present to you of actual practice there will help you to realize some of the contrasts of Maternity practice here in Britain and in South Africa and show you some of the difficulties with which we have to contend.

ENDOMETRIOSIS AND RETROGRADE MENSTRUATION

Case Report and Review

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INTRODUCTION

THE present article records a case in which gross retrograde menstruation was associated with fairly early adnexal endometriosis, and deals with two quite separate issues which this raises —namely, the relation of retrograde menstruation to pelvic endometriosis, and the criteria of an early lesion in the light of the varied reactions of the ovary to endometrial colonization.

There are, in the literature, many case reports of more or less gross retrograde menstrual bleeding following genital tract obstruction; due, usually, to a congenital anomaly, sometimes to atresia following trauma or infection, and occasionally to a tumour. Some of these cases have had associated pelvic endometriosis and some have not, the writer inferring accordingly as to the aetiological relation. A possible way to resolve the paradox is opened by the recent experimental production of endometriosis in monkeys by Te Linde and co-workers (Te Linde and Scott, 1950; Scott, Te Linde and Wharton, 1953), which brings out the importance of the latent interval. To summarize: of 10 animals in which the uterus was severed through the neck and the body displaced to produce intra-abdominal menstruation, 6 developed endometriosis after periods varying from ½ to 4½ years, 4 of them having been negative or merely suspicious at earlier biopsies; whilst 4 animals remained negative for prolonged but variable intervals. Another animal with intraperitoneal menstruation following fundectomy developed endometriosis after 2½ years, whilst 3 in which the corpus was stitched to the abdominal wall to produce either interstitial menstruation or a fistula became positive after about a year. Despite the enormous scatter, the modal interval is about a year: the latent interval in 5 of the 10 positive cases lay between 10 and 13 months. Clearly these intervals are maximal (since a positive biopsy establishes that endometriosis *has* already developed), and they need not be the same as those in women, in view of the difference of size; but it will be shown that the same temporal pattern does occur here in the published cases in question.

The existence of even a rough critical interval provides a tentative method of discovering early cases, which is independent of histology, and so of further exploring histogenesis. The purely histological criteria of earliness will therefore be discussed, in relation to the three basic reactions of the ovary to endometrial colonization. To elucidate these, a second case is reported, and 2 others briefly noted in the text. The present article supplements a previous one (Hughesdon, 1957), and has the same materials and methods.

CASE REPORTS

Case 1

Miss L.M., aged 42, was first seen on 24th August, 1955, having had menorrhagia (7–21/28) with occasional pain on the first day, for 2 years: she had previously menstruated normally and regularly (6/28) since the menarche at 14. She had had no children or miscarriages. She was found to have a slightly bulky uterus, and curettage showed an early secretory endometrium. Following this, she had 2 normal periods, and then developed very severe bleeding,

which occurred in bouts of 4–6 weeks (with intervening free intervals of a week), accompanied by pain and the passage of clots. Panhysterectomy was performed (1st November, 1956—Mr. Norman White), and convalescence was uneventful. The excised object consisted of a complete uterus (9×5·5×4 cm.) with a fibroid polyp (3×2×3 cm.) springing from the anterior wall, above which the cavity was dilated and contained blood, together with both adnexae. The serosal surface of the uterus showed some broken adhesions, and a small projecting fibroid at the right cornu. The distal part of the right tube appeared to be missing: the proximal part was without particularity. The right ovary was cystic (4×3×3 cm.), and showed broken adhesions. The distal part of the left tube was thickened and congested, with roughening of the serosa but with free fimbriae; and the left ovary (3×2·5×1·2 cm.) was rough all over.

Microscopically, the uterus showed a mild cystic endometrial hyperplasia, some right cornual adenomyosis, and a fibroid with hyaline change. The left tube showed, distally, a thick congested oedematous wall, with many lymphorrhages, together with scattered lymphocytes, eosinophils and plasma cells: the folds were swollen and the lumen contained blood (Fig. 1). The fimbrial end showed some surface endometrial islands, one of them fairly large (Fig. 2): in this, a single gland can be seen edging into the underlying muscle. A small island was found just proximally (in the distal ampulla) a short distance within the muscular wall. The interstitial part of the tube also contained blood, and showed many fine mucosal papillations, with lymphorrhages. Small endometrial islands were found in the left mesovarium, both interstitially and projecting from the surface as small polypi. The posterior surface of the left ovary showed no endometriosis: it was covered with broken, papillated and interlacing adhesions, composed of young vascular connective tissue, with some nests of siderocytes. The anterior surface facing the broad ligament showed a few similar adhesions: it was covered medially with an almost continuous narrow seam of endometrial stroma from near the mesovarium to near the antihilar border. Its varied appearances (in respect of the presence of epithelium and of blending with the underlying ovarian tissue) are shown in Figures 3 to 5. Figure 3 is from the proximal part: it shows endometrium to the right, thick above, with an attempt at gland formation, thinning into a narrow epithelium-lined seam below, presenting a fairly sharp border to the ovarian tunical tissue to the left, on which it rests. Figure 4 is from the distal part: there is seen ovarian tissue below—with a nodule of cortex proper at the left lower corner, covered by a well-defined bare stromal seam having some partially detached epithelial structures. Serial sections showed that the last continued (at right-angles to the plane of section) over a distance of ¾ mm., being attached near one end and elsewhere separating and fraying off. Figure 5 is from an adjacent region: here the seam is irregular in width and more condensed, blending with the underlying ovarian tissue and covered by rather ill-defined cubical epithelium. In all three figures the tunica bordering the endometrial carpet is very thick. In places it was slightly looser than usual: it contained only an occasional leucocyte, and stained metachromatically with toluidine blue. The right tube contained blood; and the right ovary was covered with peri-oöphoritic adhesions (as on the left, but without endometriosis).

It seems clear not only that gross retrograde bleeding had occurred in this case, but also (judging by the state of the left tube and the ovarian surfaces) that it was of some duration. The history suggests that it probably set in about 2 months subsequent to the curettage, and therefore had lasted for about a year. The associated endometrial lesions showed a gradient in degree of development (Figs. 2–5) from proximal to distal; that is, they were maximal in the distal tube, and minimal at the antihilar part of the ovary.

Case 2

Mrs. F.E., aged 56, had a panhysterectomy for a left-sided mesonephric carcinoma. This case has earlier been described in another context (Hughesdon, 1958), and the details need not be repeated: we are here concerned only with the right ovary (3×2×0·6 cm.), which

appeared grossly normal save for some light, broken adhesions.

Endometriosis of ordinary type (consisting of associated glands and stroma) was found in the mesovarium, and at two points in surface infoldings on the anterior surface of the ovary. One of these had penetrated (through a gap in the cortical tissue associated with the infolding) into the medulla: both this and the mesovarial island showed attendant areas of pseudodecidual reaction. For the rest, the whole of the anterior surface and distal part of the posterior were studded with isolated islands of endometrial stroma, variously situated, and determined by serials to be quite void of glands. Figure 6 shows two examples on the anterior surface. One of them is directly related to the right hand wall of a surface infolding, and has

TABLE I

Table of Cases with Gross Retrograde Bleeding Showing Relation to Endometriosis

No.	Age	Anatomical Background	Distribution of Retained Blood	Duration of Bleeding	Endometriosis	Other Findings	Authority
1	51	Atresia of cervix after amputation	Cervix, left tube	6 months	No	Pelvic adhesions, yellow-walled left ovarian blood cyst	Lifvendahl, 1933
2	50	Fibroid polyp occluding lumen of uterus	Uterus, right tube, pouch of Douglas	8 months probably	No	Follicle cysts	Candela, 1929
3	11	Lower vaginal atresia following vulvo-vaginitis	Uterus, left ovary	9 months	No	Reaction to bleeding only	Seitz, 1932, Case 2.
4	22	Uterus duplex bicollis, with double vagina, blind on left	Vagina, left uterine horn, left tube, pouch of Douglas	1 year	No	Adhesions	von Oettingen, 1927.
5	38	Lower vaginal atresia due to adhesions	?	1 year	Yes, pouch of Douglas	Adhesions	Scott and Te Linde, 1954, Case 4.
6	43	Cervical atresia after cauterization	Uterus	1 year	Yes, ovaries	Adhesions	Bernstein and Walters, 1939, Case 12.
7	42	Fibroid polyp occluding lumen of uterus	Uterus, left tube	About 1 year	Yes, left tube and ovary	Bilateral peri-oöphoritic adhesions	Case 1 of present article.
8	51	Partial isthmic atresia	Uterus, tube, pouch of Douglas, under diaphragm	2 years	No	Uterine adenomyosis	Bernstein and Walters, 1939, Case 18.
9	25	Cervical stenosis following delivery	Uterus, right tube	2 years	No	Adhesions	Bernstein and Walters, 1939, Case 14.
10	13	Uterus bicornis unicollis with blind right horn	Right uterine horn, right tube	About 2 years	No	Adhesions: right ovary otherwise "without alteration"	Goulart de Andrade, 1955.
11	16	Bicornuate uterus with blind right horn	Pouch of Douglas	2 years	Yes, pouch of Douglas, probably appendix	Right corpus luteum haematoma, follicle cysts	McDonald, 1943.
12	19	Atresia of lower third of vagina	Uterus, upper vagina	2 years	Yes, bladder wall, gut, omentum, tube, ovary	Adhesions	Yin, 1946.
13	19	Congenital isthmic, cervical and upper vaginal atresia	?	3 years	No	?	Hirst, 1943, p. 99.
14	17	Uterus bicornis; no cervix; transverse vaginal septum	Right uterus	3 years	Yes, appendix	Appendicular adhesions only	Plate and Rottinghuis, 1941.
15	37	Bicornuate uterus with post-infective atresia of left horn	Left tube	3 years	Yes, left tubal serosa	Peri-oöphoritis	Jacobi, 1940, Case 2.
16	22	Doubtful: immature uterus	None	4 years	Yes, utero-vesical pouch	Dense pelvic adhesions	Whitehouse, 1926.
17	28	Isthmic atresia	Left tube	7 years	Yes, right ovary	T.B. salpingitis, adhesions	Reiss, 1958, Case 2.
18	21	Bicornuate uterus, with blind rudimentary right horn	Right tube	10 years	Yes, right ovary	No	Scott and Te Linde, 1954 Case 1.
19	44	Atresia of introitus	None	14 years	Yes, left ovary, uterine serosa, right groin	Adhesions, uterine myomata	Jacobi, 1940, Case 1.
20	27	Double uterus with vaginal septum	?	14 years	Yes, right ovary	Adhesions	Granberry and Faust, 1938.
21	29	Bicornuate uterus with rudimentary left horn	Left tube	16 years	Yes, omentum, pouch of Douglas	Adhesions	Frosch, 1936.
22	31	Bicornuate uterus with rudimentary right horn	Pouch of Douglas	17 years	Yes, right uterine serosa	Adhesions	Carpenter and Jameson, 1952, Case 2.
23	49	Bicornuate uterus, no cervix, upper vaginal atresia	Left uterus, right tube	29 years	Yes, left ovary	Adhesions, uterine adenomyosis	Leverton, 1953.

FIG. 1

Case 1. Distal left tubal isthmus, showing groups of leucocytes in wall and mucosa, clubbing of folds, and blood in lumen. H. & E. ×55.

FIG. 2

Case 1. Fimbriated end of left tube, showing swollen fimbria above (largely denuded of epithelium), well-formed superficial endometrial island below, with dark U of Walthard epithelium in between. H. & E. ×28.

FIG. 3

Case 1. Anterior surface of left ovary near mesovarium, showing endometrial deposit with early gland formation above, tailing off into narrow epithelium-lined stromal seam below and to right, with thickened ovarian tunica albuginea to left. H. & E. ×120.

FIG. 4

Case 1. Anterior surface of left ovary near antihilar border, showing dark endometrial stromal seam with partially detached epithelial structures above, resting on thick ovarian tunica, with edge of dark cortex proper at bottom left corner. H. & E. ×110.

FIG. 5

Case 1. From region close to last, showing narrow irregular dark stromal seam above, covered with non-descript and ill-defined epithelium, blending below with rather loose thickened tunica. Near the bottom are 2 small epithelized surface inclusions, with the cortex proper beginning just below, especially to the right. H. & E. ×125.

FIG. 6

Case 2. Anterior surface of left ovary, with a surface infolding. The right wall of this is largely constituted by an endometrial stromal island. A separate smaller island is seen a short distance below the surface to the left of its mouth. H. & E. ×70.

FIG. 7

Antihilar pole of right ovary of a nulliparous woman of 48. The cortex is folded inwards below a miniature uterine cavity which is roofed over by adhesions. There is minimal thickening of the subjacent tunica. H. & E. ×20.

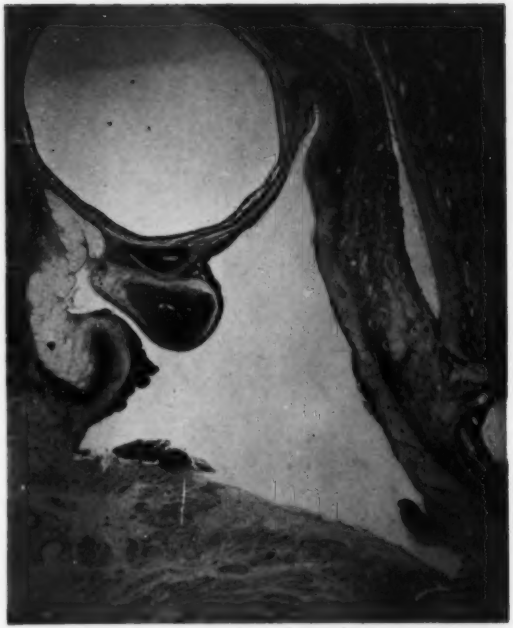

FIG. 8

Section of small left adnexal endometrial cyst from a nulliparous woman of 33. It is triangular on section, its base being formed by the wall of the tube, and its sides by the folded ovary; a diverticulum extends leftwards into a corpus albicans. Note the thick pale tunica albuginea, especially on the right. Dark cortical patches remain near the three corners, and ripening follicles are seen at top left and lower right. H. & E. ×9.

a low endothelioid surface covering, which assumes a low dark cubical form at either side. The other, seen to the left of the mouth of the infolding a short distance below the ovarian surface, is smaller, and was closely related to a tiny knuckle of infolded surface over part of its course. Both islands were cut serially from end to end, and both remained in the same topographical situation throughout. Similar islands, of varying cellular condensation and form, were found at every part of the areas noted (the whole ovary being blocked and multiply cut), chiefly at the cortex-tunica junction. Their identification as endometrial hinges on the co-existence of ordinary endometriosis, their resemblance to endometrial stroma with ordinary stains and, again, in silver preparations, which showed a characteristic thorough-going dissociation of the argentophil reticular fibrils. Most were associated at some point with a surface infolding, and with overlying loosening and light broken adhesions. The particular significance of the lesion (hitherto undescribed, so far as I know) will be discussed later.

The Literature

It is convenient to present the recorded cases of gross retrograde menstruation in which the pelvic findings have been studied in the form of a table (Table I). This summarizes the findings in 23 cases (including that described); but comment is needed on the general principle of their selection, on cases that have been omitted, and finally on some of those included.

There are three main sources of uncertainty in such material. Firstly, in deducing the duration of retrograde bleeding, one is dependent on the history (and therefore on the vagaries of the patient's memory); which is particularly serious when the intervals are short. There is a relative dearth of such cases—probably because the incentive to record them is slight. Secondly, the deduction of this duration from even an accurate history is not a secure one. This is notably true in the case of extruding fibroids, where backward bleeding may equally well have occurred for either a longer or a shorter period than the classic symptoms of extrusion. Thirdly, at operation the patient's pelvic and other viscera are not sampled with the thoroughness possible in an experimental monkey, where the detection of a possible endometriotic lesion is the only interest. Thus, if (for example) the only relevant finding is that endometriosis is not present in an excised adherent ovary, then the case is negative; though early lesions may have been present at some other point in the pelvis not sectioned. It has to be accepted therefore that the level of certainty in this material is a low one: it cannot do more than indicate general trends. For this reason I have thought it pointless to be unduly critical of the pathological identification of the lesion. If the author specifically states that endometriosis was present—or not present, then this has been accepted; unless he deliberately furnishes descriptive information suggesting a contrary conclusion. Insistence in principle on a convincing description or figure would eliminate most of the cases listed.

Certain types of case—and certain individual cases—have however been omitted. The literature of case reports of female genital anomalies (many with associated obstruction) is disproportionately large. Many have had adherent ovaries with blood cysts, which either have not been sectioned or have been reported in such terms ("simple cyst", "haematocyst") as to convey no information. It would be unjustifiable to make a presumptive diagnosis of endometriosis on the gross findings in such cases and add them to the list. Retrograde bleeding past the tubal fimbriae will be likely to cause adhesions in any case, whilst the associated inflamed ovary will be especially liable to thecal and follicular haemorrhage (judging by its behaviour in pyogenic oöphoritis). Conversely, a statement that the ovaries were macroscopically normal means almost nothing, as early endometrial lesions can be very inconspicuous. Thus, in this very large group where the author volunteers no statement as to the presence or absence of endometriosis, no independent deductions can be made from the reported gross findings. I have also not included any of the 15 cases of lateral hermaphroditism reviewed earlier (Greene, Matthews, Hughesdon and Howard, 1952). Details and references may be obtained from this article; but, briefly, 6 of

them had had intermittent lower abdominal pain, with or without external bleeding, for from 4 to 8 years, and 2 of these had pelvic endometriosis. Evidence of gross retrograde bleeding was, however, minimal or lacking: none had retained blood in the uterus or tube. Another class of case wholly omitted is that in which the clinical and operative findings (pain, with tubal and pelvic blood) suggest a disturbed tubal pregnancy, but section fails to discover an ovum. Examples are recorded by Schmid (1925), who reviews the early literature, and more recently by Balmary and Isidor (1949). Whether this syndrome is really due to an unrecognized tubal pregnancy or not, it seems likely that the blood has come from the tube rather than the uterus.

Individual cases omitted are those of Bernstein and Walters (1939, Case 1), Clark (1948), and Te Linde (1953): all 3 had pelvic endometriosis in association with gross retrograde menstruation, but in none can the duration be deduced from the recorded history. Another omission is the case of Vernaglia (1948), which was not one of retrograde menstruation and had an odd anatomy; but the omission must be justified in detail, as the case is a theoretical misfit. A girl of 12½ was operated on during her third known menstrual period: she was found to have a bicornuate uterus, the left half of which opened through a cervix into a normal vagina. The right uterus opened through a lower orifice (described as a cervix) 0·4 cm. in diameter into a pear-shaped blood cyst (7·5×10 cm.) beneath the pouch of Douglas. Section of the cyst wall showed fibrous tissue, covered internally with red cells, siderocytes, and "with tissue that had the appearance of endometrium"—described later as "consistent with an endometrial implant": there is no mention of vaginal epithelium. Blood was present in the uterus (which showed a hyperplastic endometrium) and in the right tube. It would seem almost certain that the blood cyst resulted from the ballooning of a pre-existing epithelium-lined cavity, probably of uterine—and possibly adenomyotic—origin, and that the "implant" represented the remains of its lining; for one cannot suppose that the uterus opened interstitially into the pelvic cellular tissue *ab initio*, and if it produced such an opening through rupture, one would normally expect, not just a discrete walled blood cyst, but also extensive interstitial haemorrhage. The case of Williams (1924), with nearly 30 years amenorrhoea and periodic pelvic pain, is omitted, though it has been cited against Sampson's theory; for there needs to be some indication that the retained blood got past the tubal fimbriae, evidenced by blood and/or adhesions beyond this point. Here, however, the author specifically remarks: "The entire absence of adhesions round the Fallopian tube does not support the idea that the menstrual fluid escaped by that route."

Six of the included cases call for comment. Candela's case presents the usual difficulty as to the time interval associated with an extruding fibroid. A multiparous woman of 50 had had normal periods until 8 months before operation. Her periods then became abundant, and she also developed intermenstrual bleeding: 2 months before operation the bleeding became less severe. The operative findings are given in the table; and it may be inferred that retrograde bleeding had occurred for 2 months, and probably 8 months. The case of Seitz was regarded by him as positive, and is here entered as negative: the issue turns entirely on the interpretation of the blood cyst of the left ovary—as to which Seitz remarks "The microscopical investigation of the chocolate cyst of the excised ovary yielded no faultless evidence of endometrial tissue". He nevertheless inferred that it was endometrial, on the strength of some unfigured loose stroma, epithelioid cells, siderocytes and lymphocytes, in a brief account which conveys no more than the inevitable reaction to bleeding. In Goulart de Andrade's case the interval (entered as "about 2 years") may have been anything from 1 to 3 years as we are told only that the patient had the menarche at 11 and was operated on at 13. Hirst's case report is unusually brief, giving little detail—and none to suggest that blood had passed the tubal fimbriae. I have included it, as it is expressly stated that the patient had "presumably for 3 years been menstruating painfully into the peritoneal cavity"—though the grounds of this presumption are not mentioned. Plate and Rottinghuis did not think that their case could

reflect retrograde menstrual bleeding, because there were no general pelvic—as opposed to appendicular—adhesions. Nevertheless I have thought it justifiable to include it, in view of the particular ease with which trouble emanating from the pelvis may preferentially assault the ileo-caecal region (for example, in recurrent ovarian carcinoma). In Reiss's case the essential diagnostic finding was a blood cyst partly lined by a narrow stromal seam surmounted by epithelium (as in Figure 3, bottom right). This is the commonest lining to an endometrial cyst, being frequently described by Sampson (1921) and later writers. An interrupted inner cortex was readily demonstrated by multiple sections.

Discussion

There are two separate matters to be discussed, namely, retrograde menstruation and the reactions of the ovary—the temporal and spatial contexts respectively of endometrial colonization.

(1) *Retrograde Menstruation.* The temporal pattern shown by the table is broadly similar to that in experimental monkeys; for it seems that a certain latent period must elapse before endometriosis can develop at all, and the likelihood of getting it increases progressively with the interval. This could be put in various ways—for example, 10 out of 11 patients with retrograde bleeding for 3 years or more had endometriosis, whilst of those with an interval of 2 years or less 5 out of 12 had it. The increase in the incidence does not progress smoothly with the increasing time interval, but neither did it in the monkeys: moreover (apart from the uncertainty of the medium) this is easily explained, for example, by variations in amount of the retrograde bleeding. The finding has three implications.

Firstly, the addition of even this rough quantitative factor to the existing qualitative items of evidence decidedly strengthens the view that there is a correlation between retrograde menstruation and pelvic endometriosis.

Secondly, the long latent interval calls for explanation, and four possibilities suggest themselves. The *first* (suggested by analogy with the long latent interval of tumour induction) is that regurgitated endometrium does not in fact implant, but exerts an inductive effect on the serosal or mesenchymal host tissue, causing it to turn itself into endometrium. Such a view would neatly reconcile the lines of evidence for a local and for an implantation origin; but the postulated pattern of events (induction of like by like) is almost without biological precedent. Nevertheless, experimental evidence has been provided for it by some Swedish work (Levander, 1941; Palmstierna, 1943; Levander and Normann, 1955), which has not attracted the attention it deserves. It is claimed that pieces of pregnant rabbit uterine wall, transplanted subcutaneously, do not survive (as generally supposed), but die entirely: what is later found is regenerated anew by the surrounding connective tissue, chemically influenced by the dying transplant. Unfortunately, the actual findings are open to other interpretations, as Palmstierna notes; but the negative or doubtful early biopsies (consisting of simple epithelial rings and the like), found by Te Linde and co-workers in experimental monkeys, could most readily be explained as an incomplete or early inductive effect. The *second* is that the amount of tissue actually able to implant at any moment is minute, so that time is needed for it to grow enough to become recognizable: this is suggested by analogy with scar endometriosis, where also the interval may be long. Both the finding of Haselhorst and Otto (1930) that a small thread of endometrium may percolate from the uterus along the line of least resistance afforded by a stitch-track, and Sampson's (1945) finding that the mediating element may be a long narrow tubal sprout, suggest this simple mechanical explanation. The *third* is that time is required to prevail against the inhibitory influence of "menstrual toxin" (Smith and Smith, 1946), which seems incalculable; and the *fourth* that it is needed to roughen the ovary or serosa and permit implantation, for which it seems too long. These factors are not mutually exclusive, and I shall not pretend to settle the point by argument.

Thirdly, this variously evaluated latent interval (critical, but vague) of 1–3 years may well be longer if retrograde bleeding is less gross. Fallon (1946), in a study of 9 teenage cases of

endometriosis, found the interval from the menarche to vary from 2 to 9 years, with a mode of about 5. This was probably the duration of any retrograde bleeding; for, as there is no mention (and no *a priori* likelihood) of gross uterine pathology, the disposition to bleed in this way would then be intrinsic. Recently, Scott and Wharton (1957) have reiterated that 5 years of menstruation uninterrupted by pregnancy expose the susceptible to the risk of endometriosis: these might be persons subject to retrograde bleeding for (in the light of the table) such reasons as minor uterine malformations or tumours protruding slightly into the cavity. However, the duration of such bleeding cannot be dated, even approximately, except in the young or in those with genital obstruction; and in these the critical interval offers a possible independent check that a lesion which seems histologically early may in fact be so. It is convenient therefore at this point to consider the purely histological criteria of earliness, by reconsidering the histology of Case 1 (which seems to be only moderately early) and of certain other cases.

(2) *Reactions of the Ovary.* At first sight, Case 1 seems likely to present early lesions, for the presumptive time interval is short. Clearly those either on (Fig. 2), or in, the distal part of the tube are not early, but (as remarked) there is a gradient (Figs. 2–5) in the degree of development of the lesion from here to the antihilar part of the ovary. This might be expected in a fairly early case; for the fimbrial ciliary currents will tend to clear them of irritant debris, so that these come to rest (like flotsam and jetsam) at the fimbrial margin (as in Figure 2), where endometrial development is maximal. (A similar mechanism doubtless keeps the tubes patent in advanced cases. The fimbrial margin is a favourite site for early lesions: Sampson (1932) described 11 such cases, under the title of "fimbrial endometriosis", but ascribed them to metaplasia rather than implantation.) Thereafter, seepage will occur slowly downwards between the anterior surface of the ovary and the broad ligament; so that minimal lesions may be expected near the antihilar border of the ovary. Figure 5 might be such a lesion, its condensed and rudimentary structure—coupled with its fusion with the underlying ovarian tissue—rather favouring a local origin by induction. Figure 4, from nearby, suggests on the contrary that the rudimentary character is secondary, and results from the difficulty of the stroma in this position in holding its epithelium. One can as easily visualize Figure 4 turning into Figure 5 as *vice versa*, and there is nothing whatever in the lesions (considered in isolation) to decide between the two possibilities.

The essential principle here is that a rudimentary lesion is not necessarily an early one (though the converse must be true): it is necessary that the ovarian reaction be rudimentary also. An important feature of these lesions (indicative of age) is the very thick tunica albuginea underlying them. An idea of its thickness may be got from Figures 4 and 5, for the darker and more cellular cortex proper is only just beginning at the left and right lower corners respectively. Both the cause and the effect of this thickening deserve consideration. Only a small part of the cause can have lain in the loosening of this tissue, for this was of minor degree (cf. Fig. 3): it certainly did not lie in the post-inflammatory production of new connective tissue, for there was virtually no evidence of inflammation. The basic cause lies, I believe, in a fundamental property of ovarian tissue of compensating an enhancement of cellularity at one point by a reduction nearby. This property I infer on general grounds: if it were not present, the ordinary processes of follicle maturation (which include granulosal, thecal and stromal proliferation) would result in a progressive growth of ovarian size throughout reproductive life. In the present context, the element of enhanced cellularity is provided by the endometrial stroma growing on the surface; and this view implies that the ovary comes to treat this as part of itself in a more fundamental sense than that of simply giving it a blood supply.

The effect of the reduced cellularity and consequent tunical thickening may be expected (on the analogy of the behaviour of scar tissue) to be contraction, with buckling and folding of the ovary; and this will be enhanced if there has been a simultaneous or prior reactive proliferation of the underlying cortex, so that shortening

of the surface is complemented by elongation of the sub-surface. The anatomical result will depend on how much of the ovarian surface the endometrium has managed to colonize before the buckling process sets in. If (as in Case 1) this is extensive, the folding will affect a large part of the surface; so that the ovary as a whole will curl up (like a dead leaf) round the endometrial area, and form thereby a typical large endometrial cyst. It has been shown that such cysts are on, and not in, the ovary (Hughesdon, 1957); and if Figure 5 of this article be referred to, the relatively thick tunica bordering the cyst lining will be noted. This I believe to be the most important single factor creating an endometrial cyst.

The inferences made (in the light of Case 1) as to the reactions of the ovary to endometrial colonization have been largely abstract: two items of evidence may now be mentioned. Firstly, one case in my series—a nulliparous woman of 33—had a typical chocolate cyst of the right ovary, but showed on the left a structure intermediate between such a cyst and the ovary of the present Case 1. The left ovary, which was of normal size and stuck medially on to the uterus, had folded partially, so as to enclose a small blood-filled cavity against the adjacent broad ligament and tube. Figure 8 shows a section through its middle, where it has roughly the form of an equilateral triangle, with the base furnished by the tube wall and the sides by the folded ovary. In addition, a diverticulum on the left has penetrated through the site of a follicle rupture into the middle of a corpus albicans. Most of the lining consists of the usual narrow seam, but more substantial endometrial islands can be seen below on the tube. The thick pale tunica bordering the lining is clearly visible, especially on the right. The underlying cortex has partly involuted, but dark residua are seen near the three corners: late ripening follicles are seen to the left above and to the right below. This case establishes that folding of the ovary occurs, as postulated, in association with thickening of the tunica; but not, of course, that this thickening is the efficient cause. However, and secondly, a thick submucosal tunica (often bordering a thin and interrupted inner cortex) is a common and characteristic feature of an endometrial cyst. Of my 29 cases, 21 were classed as large (due to folding of most of the ovary) and 8 as small (due to cystic distension of a gland in a pre-existing pit). Of the former, 19 showed a thick submucosal tunica; and of the latter 6 did so (3 markedly, 3 patchily or slightly). On the other hand, of 30 lesions described as surface pits and plaques, 18 showed no thickening of the subjacent tunica at all, 11 showed it moderately, and only Case 1 of this article showed it markedly. In general, the deepest pits had the thickest tunicae, but these lacked the gross reduction of cellularity, and consequent contrast with the subjacent cortex, found round endometrial cysts. An average instance is seen in Figure 7—a symptomless antihilar pit in a nulliparous woman of 48: it consists of a miniature uterine cavity, roofed over by adherent new connective tissue, and lying in a fold in the ovarian cortex. There is a very slight thickening of the subjacent tunica, inasmuch as a pale hypocellular zone is recognizable here and not round the outside. It seems reasonable to attribute this topography mainly to a prompt proliferation and consequent buckling of the cortex, the elongation of which is apparent—still more so in the deeper pits. Thus, a thick submucosal tunica seems to bear a particular relation to an endometrial cyst; and the findings suggest that the difference between this and the other lesion is not one of age but of mechanism—a reflection of the speed of ovarian reaction in relation to that of colonization. A prompt reaction is probably better for the patient and leads to local buckling into a small pit: a more tolerant ovary allows more extensive surface spread, thickens its tunica and folds, resulting in an endometrial cyst. I would add that in my material the age distribution of the two lesions was about the same, which does not suggest that one is an early form of the other.

It is clear that both these reactions (as shown in Figures 7 and 8) are quite gross, and that neither can possibly be an early lesion. Figure 6 shows a lesion of a different sort, having no necessary relation to folding of any part of the ovary. It is clinically silent and therefore presumably the most favourable for the patient;

and as both the lesion and the ovarian reaction are minimal, it is probably the earliest of all. Though undescribed, it is fairly common in the forties and fifties. What seems to have happened is that isolated stromal islands (which may have shed their epithelium in the manner of Figure 4) have arrived at the ovarian surface, acquired a protective covering of ovarian epithelium, and then been incorporated into the surface and sub-surface regions of the ovary—presumably by prompt differential proliferation of a very local kind. Most of these islands were found, in my material, at the cortex-tunica junction. The overlying ovarian surface might be quite smooth, or might show local loosening, light adhesions, and local infoldings. A smooth surface might seem to favour a local (as e.g., inductive) origin as opposed to implantation; for it is difficult to see how an implant could reach the interior without disturbing the surface. However, the deduction is unsound, as the same occurs with secondary carcinoma of trans-serosal origin. In the abstract the lesion is compatible with either explanation: its detailed study, in my material, favoured a local origin for several reasons, but indecisively. It would therefore be inexpedient to pursue the matter into details here.

In conclusion, the general position may be summarized thus: there is good evidence of a correlation between the occurrence of retrograde menstruation and pelvic endometriosis, but whether this is mediated by implantation and/or induction is unknown—this being the outstanding unsolved problem. The ensuing ovarian lesion is always on the surface—as might be expected—insofar as it is fully formed of associated glands and stroma; and its varied form reflects variations in the relative speed of endometrial colonization and of the ovarian reactions. A third minimal lesion consisting of isolated islands of endometrial stroma also occurs at the ovarian surface and sub-surface: as the associated ovarian reaction is also minimal, it may be presumed to be early. Its detailed study may throw further light on histogenesis, especially in a context (dated genital tract obstruction for 1–3 years) which independently suggests earliness.

Summary

(1) Two case reports are presented—one of fairly early adnexal endometriosis following about a year's gross retrograde menstrual bleeding, and one of a rudimentary, presumptively early, hitherto undescribed lesion, consisting of isolated stromal islands at the ovarian surface and sub-surface.

(2) A review of the literature of gross retrograde menstruation due to genital tract obstruction suggests that the presence or absence of associated pelvic endometriosis depends on its duration, with an apparent critical interval of from 1 to 3 years. This corresponds with the temporal pattern in experimental monkey endometriosis, and fortifies the presumption of a correlation between retrograde menstruation and pelvic endometriosis.

(3) Possible reasons for the long latent interval are considered, the suggested ones being the local production of endometriosis by induction rather than by implantation, the viable implantability of only minute fragments, the inhibitory effects of "menstrual toxin", and the need to induce a receptive state in the host tissue.

(4) The reactions of the ovary to endometrial colonization are discussed. The two main ones are cortical proliferation and buckling (producing surface pits) and tunical thickening, contraction, and ovarian folding (producing endometrial cysts): neither of these lesions is early.

(5) The rudimentary lesion of Case 2 is probably early, as the associated ovarian reaction is equally rudimentary. The intensive study of such lesions may further illuminate histogenesis.

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ANALYSIS OF NEONATAL MORTALITY

With Special Reference to the Incidence and Results of Foetal Apnoea

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I HAVE presented below an analysis of stillbirths and neonatal deaths recorded in 16,586 consecutive deliveries at Woking Maternity Hospital in the 15 years 1943–1956. During this period modern antibiotics and adequate supplies of blood have been available and the great adjustment to modern conditions of obstetrics has been complete. My first objective has been to make a careful analysis of hospital population, stillbirths and neonatal deaths by age, gravid rank, clinical cause, etc., to show the main features of foetal loss. This series is of special interest and indeed exceptional, since only the simplest methods of treatment have been used in the management of newly-born infants, and the same methods have been continued throughout the whole period. I hope, therefore, that such an analysis may give useful information and by comparison with the results of other hospitals, may provide some help in assessing the value of resuscitation procedures in newly-born infants. The analytical tables are arranged, as far as possible, to allow comparison with the extensive series recently reported from Aberdeen Maternity Hospital (Baird *et al.*, 1954) which deal with the stillbirths and first week deaths of 26,116 booked single births delivered in the hospital. In comparing results in this way, it is necessary to remember that hospital populations vary greatly in composition and in obstetrical complications, and problems differ in different areas and details of obstetric technique cannot be analyzed. These difficulties are common to all efforts at statistical analysis of clinical problems, but I believe that this attempt is worth making and that helpful findings will emerge. In the second section of this paper, I have tried to show in greater detail the clinical effects of foetal apnoea ("asphyxia") of varying duration upon the survival of mature and premature infants.

In making the classification of stillbirths and of neonatal deaths I have followed the indications and with a single exception I have adopted the categories recognized in the analysis of the series from Aberdeen already referred to. The exception is the substitution for the "Other Causes" category of a group for foetal and infant disease, which includes cases of Rhesus incompatibility, infections, etc. The following categories are recognized:

(1) Premature, cause unknown: normal pregnancy and labour and normal foetus apart from weight of 5½ pounds or less (2,500 g.). This category includes many small infants who die with the "pulmonary syndrome" with or without hyaline membrane or intraventricular cerebral clot.

(2) Mature, cause unknown: infants over 5½ pounds in weight and cause of death obscure. In this and in the preceding category I have made a distinction whenever possible between intra-uterine death with maceration and intrapartum death with delivery of a fresh foetus.

(3) Trauma: death of the foetus or infant associated with abnormal presentations (including breech presentations), cord complications, prolonged or difficult labour and when evidence of physical trauma is revealed by post-mortem examination.

(4) Toxaemia: this is taken as the primary cause of death in eclampsia and in pre-eclampsia (pregnancy toxaemia) when there is albuminuria of more than 0·05 per cent. Cases of accidental haemorrhage with albuminuria are included in this group.

(5) Ante-partum haemorrhage: cases of indefinite bleeding when a material amount of blood is lost, of declared placenta praevia and of accidental haemorrhage without albuminuria.

(6) Maternal disease.

(7) Disease of the foetus or infant.

(8) Deformity, when incompatible with life. When present this is taken as the primary cause of death.

It is to be noted that there is no category for "Prematurity, *per se*", and the term "Premature, cause unknown" refers to the cause of the prematurity and not to the direct cause of foetal or neonatal death. It may be extremely difficult to decide upon the correct category for any given case, and not uncommonly more than one factor is present. Cases in which labour has been difficult or prolonged for 36 hours or more are classed as traumatic deaths (stress asphyxia). The importance of hypertension, when albuminuria is slight or absent, is not easy to assess. The inclusion of cases of accidental haemorrhage (*abruptio placentae*) with albuminuria in the toxaemia category is open to objection, but such difficulties are unavoidable in any system.

Hospital Population

While it is not possible to give the social grading of all patients admitted, some information about local conditions will be useful. The hospital contains 54 beds, a small number for the district served, and cases for admission have been carefully selected throughout the period under review, in order to provide beds required for abnormal and emergency work. Normal cases have been restricted to a limited number of primiparae and to multiparae admitted on account of poor social conditions. With the exception of some evacuee mothers sent down from London during the last War, it is generally true that the hospital population is well-fed, well-clothed and with sufficient money to provide all necessities. It is not common to meet a woman with more than 4 children and smaller families are the rule. While serious pelvic deformity is rare, borderline disproportion is not uncommon. Woking is essentially a residential area, but there is much industrial activity in the neighbourhood, including the very large engineering works of Vickers at Weybridge, and there are many large factories at Egham which is also served by the Hospital. Extensive permanent caravan populations are installed at Addlestone and Chertsey.

Post-partum Management of the Infant

The following procedure has been standardized during the period under review. Unless the infant cries immediately, it is placed in a cot or upon a low table (e.g., after Caesarean section) with the head a little lower than the heels and turned slightly upon the right side. Special care is taken to see that the head is thrown back, and that the airway is not blocked by a depressed chin. Great importance is attached to maintaining the correct position. The face is wiped clean of blood and mucus, and occasionally, if the child is very collapsed, the tongue is held forward with a small clip. The infant is wrapped in a light blanket, but no attempt is made to give artificial heat. Stimulants (coramine, lobeline, etc.) are not used. No attempt is made to give oxygen in the delivery room. If breathing is not entirely satisfactory after 10–15 minutes, the infant is removed to the nursery, covered with a Queen Charlotte's Hospital perspex box, and additional oxygen is run through in a gentle stream for as long as is considered necessary. In all cases, oxygen is given only "on demand" and for the shortest possible time. Infants are nursed in cots—incubators are not used.

In compiling the tables that follow, it is important to remember that there has been a nation-wide reduction in the proportion of stillbirths and neonatal death for some years. The rate of perinatal loss for the first 4 weeks reported by the Registrar General (1956) has fallen steadily from 59 per 1,000 total births in 1943 to 47 per 1,000 total births in 1955, the last year for which full statistics are available.

GENERAL HOSPITAL STATISTICS 1943–1956

Total number of deliveries		16,586
Single births only	16,305	
Multiple births	281 (3 triplets)	
Total number of infants born		16,870
Premature infants born (7·2 per cent of deliveries)		1,217
Single pregnancies only	915	
Stillbirths, including multiple births: 377 in 16,870 deliveries	22·3 per 1,000 total births	
Stillbirths, single births only: 343 in 16,305 deliveries	21·0 per 1,000 single births	
First-week infant deaths, single births only: 224 in 15,963 single deliveries	14·0 per 1,000 live births	
Neonatal deaths (including multiple births) first 4 weeks: 292 in 16,494 deliveries	17·7 per 1,000 live births	
Infant loss (stillbirths+first-week infant deaths) single births only: 567 in 16,305 deliveries	34·7 per 1,000 single births	
Perinatal mortality (stillbirths+infant deaths) first 4 weeks, including multiple births: 669 in 16,870 deliveries	39·6 per 1,000 total births	

These results include booked and emergency cases. The overall infant mortality from stillbirths and first-week deaths reported by Baird *et al.* from Aberdeen for 1938–52 (booked single births only) was 38·6 per 1,000 single births.

Perinatal mortality for the City of Birmingham 1951–1955 only, with 91,656 births, is recorded as follows by Crosse (1957):

Stillbirth rate	22·6 per 1,000 total births
Neonatal death rate	17·1 per 1,000 total births

These figures give an overall mortality rate of 39·2 per 1,000 total births including hospital and domiciliary confinements.

TABLE I

Analysis of Hospital Population by Maternal Age and Gravid Rank, 1943–1956

Age	Gravida 1	Gravida 2+3	Gravida 4 and Over
15–19 years	702	86	1
20–24 years	3,149	1,328	58
25–29 years	2,417	2,281	311
30–34 years	1,107	2,028	506
35+ years	618	1,269	725
	7,993	6,992	1,601

Total deliveries: 16,586.
Multiple pregnancies: Gravida 1 104.
Gravida 2–3 133.
Gravida 4+ 44.
Total: 565 infants (3 triplets).

TABLE IIa

Tabulation of Stillbirths and Neonatal Deaths by Clinical Causes

	Single Births				Multiple Births		
	Still-births	Macerated Foetuses	Neonatal Deaths 1 Week	Neonatal Deaths 4 Weeks	Still-births	Neonatal Deaths 1 Week	Neonatal Deaths 4 Weeks
Premature, cause unknown	47	(40)	41	3	13	19	5
Mature, cause unknown	42	(30)	8	1	2	—	1
Neonatal disease	10	(5)	22	6	—	—	3
Antepartum haemorrhage	34	(6)	30	3	2	1	–
Pregnancy toxaemia	32	(13)	31	3	1	5	–
Trauma	87	—	55	2	14	8	–
Maternal disease	7	(5)	2	–	—	—	–
Deformity (lethal)	76	(?)	43	8	2	—	–
	335	(99)	232	26	34	33	9

N.B.: Macerated foetuses (intra-uterine foetal death) refers to the totals of stillbirths in the preceding column.
Forty-two small prematures (11 twins) with weights of 2 pounds or less are included in this Table.

TABLE IIb

Stillbirths and First-week Infant Deaths by Clinical Causes: Percentage Distribution
(Excluding Multiple Births and B.B.A.)

	Gravida 1	Gravida 2+3	Gravida 4+	All	Aberdeen
Premature, cause unknown ..	18·4	12·9	13·5	15·5	19·7
Mature, cause unknown	10·1	8·5	5·6	8·8	13·7
Trauma	30·0	18·5	25·8	25·2	18·8
Pre-eclampsia	13·9	9·0	6·7	10·9	10·0
A.P.H. (non-toxic)	6·0	13·7	21·3	11·2	10·9
Deformity (lethal)	17·3	25·4	21·3	21·0	15·6
Maternal disease	2·2	0·4	1·1	1·6	6·0
Infant disease	1·9	10·8	4·5	5·6	5·3
Total cases reviewed	266	212	89	567	
Infant loss per 1,000 single births ..	33·9	30·9	56·4	34·7	
Infant loss per 1,000 total births ..	33·2	30·3	55·6	34·2	

All infants in the group "Mature, cause unknown", were examined post-mortem. In the group "Premature, cause unknown", 17 infants, all small prematures, were not examined if death occurred within a few hours of birth. Small and feeble prematures and infants dying with signs of the pulmonary syndrome have been allocated to this group in the absence of maternal toxaemia, A.P.H. or other clear cause of death. Asphyxial signs, hyaline membrane and intraventricular cerebral haemorrhage have been disregarded. Comparison with the Aberdeen series shows almost identical proportions for infant disease, ante-partum haemorrhage and for pregnancy toxaemia. In this last category are placed 6 cases of infant loss following marked maternal hypertension with slight albuminuria. Such cases are not included in this group in the Aberdeen series, but it seems misleading to place them in the group of foetal death "cause unknown".

Further comments may be made as follows, with special reference to mature infants.

Mature, cause unknown. At 8·8 per cent the overall figure is definitely below that reported from Aberdeen. Eight infant deaths are recorded, approximately 1 in 2,000 births. Post-mortem examination was made in every case. Four infants lived for 3 days or longer, and appeared normal at birth. Of the others, one delivered by Caesarean section and one delivered spontaneously cried well and seemed normal and healthy at birth. One other delivered by section and one delivered by forceps did not breathe well and these two were never satisfactory although in both cases regular breathing was established and maintained for several hours.

Premature, cause unknown. At 15·5 per cent the overall figure is again below that reported from Aberdeen, where mature and premature infant losses together, from unknown causes, was nearly 10 per cent above the total for the present series. The lower figure at Woking may represent the general reduction in infant mortality that has occurred in recent years. Crosse (1954, p. 66) records only 11 per cent of perinatal deaths, cause unknown, in the Birmingham series for 1952, for mature and premature births, but this figure is not strictly comparable, since this author recognizes a category for Prematurity *per se*. It is especially interesting to notice the rarity at Woking of stillbirth, cause unknown, in fresh foetuses both mature and premature.

Trauma. The infants were mature in 30 out of 56 neonatal deaths recorded. Of these 26 showed evidence on post-mortem examination of such extensive intracranial trauma that it seems unlikely that resuscitation would have been helpful. Two others were delivered by forceps,

in one of which the umbilical cord was broken during delivery, but evidence of intra-cranial trauma was rather equivocal. One other infant survived for three days and died with fits. In this case no post-mortem examination was made, and intracranial trauma was diagnosed upon clinical grounds.

Pregnancy toxaemia. Of the 30 neonatal deaths recorded in this category, the single mature infant died with convulsions on the fourth day. At birth it behaved normally. Unfortunately no post-mortem examination was made in this case.

Ante-partum haemorrhage. Of 30 neonatal deaths recorded the infants were mature in 2 cases. In one delivered by Caesarean section after accidental haemorrhage (*abruptio placentae*), the infant was in poor condition at birth, frothed at the mouth and failed to cry. It died in 24 hours. In the second case, also following accidental haemorrhage, delivery was spontaneous. The infant failed to cry and died in 12 hours. In both cases post-mortem examination showed anoxic signs, but no gross pathological changes were found.

Deformity. The higher figure of 21·0 per cent of deaths due to lethal abnormality is not due to excess of abnormals (115 infants). This number represents only 0·7 per cent of total admissions. Malpas (1937) reported about 1·0 per cent of abnormals in his series from Liverpool and in the Birmingham series for 1952 (Crosse, 1954) the infant deaths due to deformity are given as 21·4 per cent of the total.

Neonatal disease. Twenty-two neonatal deaths are recorded, of which only 3 occurred in prematures. In the case of 9 of these infants death was due to "pneumonia", as established by pathological examination and microscopic examination of lung tissue which was carried out in all cases. In 6 cases the infants died as a result of Rhesus factor incompatibility, and the remaining 6 infants all died from various well-defined morbid conditions not associated with post-partum apnoea.

This analysis of foetal and infant loss in 16,305 single pregnancies shows totals for first-week deaths and for neonatal deaths that are comparable with the overall figures reported for similar groups of cases by other hospitals. I think it may be said that the results achieved by adopting an expectant attitude during the phase of neonatal apnoea have been satisfactory. No evidence of increased foetal loss appears in this crude analysis as a result of the very simple and conservative methods employed during the immediate post-partum period.

The special features of the survival of prematures may be approached from another angle. The survival rates of infants of various weights in this series may be compared with series from other hospitals which have been analyzed with greater precision. A suitable analysis is that published by Dr. Mary Crosse (1957) for the Sorrento Premature Infant Unit, Birmingham. Dr. Crosse tells me that the treatment of these infants is conservative, the airway is cleared if necessary, and intra-gastric oxygen is given if cyanosis develops. In very occasional cases the phrenic nerve stimulator is used. Another suitable analysis is that published by Dr. Edith Potter (1954) for prematures at the Chicago Maternity Hospital. This latter report is of special interest, since it may be assumed that active measures of resuscitation were employed in every case. In making such a comparison, many factors will be present that must defy analysis, such as different obstetric and nursing techniques, different hospital facilities, etc. In the following Table (Table IIIa) I have given first a close analysis of premature first-week infant deaths, single births only, at the Woking Maternity Hospital, followed by a comparative table of the total neonatal deaths (first four weeks) on a percentage basis, to show results for similar periods at the Sorrento Maternity Hospital at Chicago and at Woking.

These tables for neonatal deaths show results for the first three categories that are very similar for all three hospitals. In the case of the largest infants, weight group 2,000 to 2,500 g. the results at Woking are disappointing, and further analysis shows that the causes of the infant deaths were as follows: 3 infants, apparently normal at birth, died with the pulmonary syndrome on the second, third and fourth days after birth; 2 infants died after delivery by Caesarean section for placenta praevia; 1 infant died after delivery by Caesarean section for maternal toxaemia; 6 infants died from birth

TABLE IIIa

Neonatal Deaths (First Week only) at Woking Maternity Hospital, Premature Single Births

Weight Limit	1943–1950			1951–1956			1943–1956		
	Total Births	Died	Per cent	Total Births	Died	Per cent	Total Births	Died	Per cent
1,000 g.	20 (15*)	19	95	29 (17*)	25	86	49	44	90
1,500 g.	43 (1)	22	51	44 (1)	24	53	87	46	52
2,000 g.	82 (2)	22	26·5	112 (3)	15	13·4	195	37	19
2,500 g.	282 (4)	14	5	317 (5)	14	4·4	599	28	4·7

* Figures in brackets indicate very small prematures of 2 pounds weight or under.

(1) Includes 1 infant with lethal abnormality.

(2) Includes 2 infants with lethal abnormality.

(3) Includes 2 infants with lethal abnormality.

(4) Includes 7 infants with lethal abnormality.

(5) Includes 5 infants with lethal abnormality.

TABLE IIIb

Neonatal Deaths, First Four Weeks, Including Multiple Births

Weight Limit	Sorrento Maternity Hospital (1) 1951–1956		Chicago Maternity Hospital (2) 1947–1952		Woking Maternity Hospital 1951–1956		
	Total	Died Per cent	Total	Died Per cent	Total	Died	Per cent
1,000 g.	13	69·2	60	98	42	37	88
1,500 g.	29	48·3	127	50	62	32	50
2,000 g.	94	18·1	220	16·3	161	23	14·3
2,500 g.	370	3·5	858	2·5	362	19	5·2

The infant loss at Woking from lethal abnormality remains as specified in the Table IIIa.

(1) Crosse, 1957, p. 224.

(2) Potter, 1954.

trauma (3 single pregnancies, 3 twins); 1 infant died on the sixth day from peritonitis; 1 infant died on the seventeenth day with pulmonary abscesses; 5 infants died with lethal abnormalities.

Most of these deaths were surely not preventable, and the high infant loss is rather related to exceptional difficulties and unusual complications.

The exact objectives of resuscitation are rarely defined with precision. The claims made by implication may fall under two headings, viz.:

(1) Assistance in the initiation of breathing and rescue of an infant who would otherwise die in apnoea.

(2) The prevention of possible nervous sequelae which might develop in later years as a result of prolonged apnoea.

In this connexion I have decided to use the term foetal apnoea in preference to asphyxia for the common phase of post-partum respiratory delay, but neither term is very satisfactory. Usually the apnoea is not absolute, but is interrupted by gasps at longer or shorter intervals, while asphyxia is also used for an

entirely different condition of suffocation in adult individuals. It cannot be doubted that conditions in the immediate post-partum phase, when some features of the foetal physiology doubtless persist, are quite unlike anything that is met with in later life. A special term for delay in establishing regular breathing at this time would be useful in preventing confusion with respiratory difficulties in established infants. In the following tables it is assumed that the phase of foetal apnoea lasts until regular breathing is established, i.e., during the phase when complete inertia is interrupted by occasional inspiratory gasps. A distinction is to be made between resuscitation during this phase, which includes attempts to improve the oxygenation of the blood before the onset of natural breathing, i.e., during the last phase of foetal physiology, and, on the other hand, administration of oxygen after the onset of respiration, by placing the infant, no longer a foetus, in an oxygen-rich atmosphere. The problems raised by the possibility of damage to brain tissue by foetal anoxia are very involved and these are not considered in this paper. The more obvious possibility of assisting a newly-born infant during the phase of foetal apnoea can be examined with greater confidence. Clinical analysis should give valuable help in settling two important questions:

(1) Do infants born alive ever fail to breathe in the absence of grave birth injury or physiological defect?

(2) Do infants who remain for a long time in foetal apnoea show a higher neonatal mortality than those who establish regular breathing quite quickly?

(1) In a recent article it is stated (Gairdner, 1954): "The number of infants with severe apnoea, who will survive only if special measures are applied, is small." Since the practice of active resuscitation seems especially applicable to this group it is of great interest to estimate the proportion of newly-born infants for whom special measures may be vitally necessary. An infant which shows signs of life is to be judged live born. From time to time infants are born with good cord pulsation who nevertheless fail to breathe, or at least they fail to establish respiration and cannot achieve anything more than foetal gasps. In making the present analysis, I have been surprised to discover how rarely this happens. During the last 14 years, I have found records of only 8 cases in which an infant born with signs of life has failed to establish regular breathing. In 6 of these cases post-mortem examination showed signs of gross intracranial trauma, of which the following is a typical example:

1953. 9th January. No. 21. Primipara, aged 27. Delivered normally at term after labour for 5 hours. The infant, which weighed 8 pounds 12 ounces showed good pulsation of the cord, but only occasional gasps were made and the child died in 40 minutes. Post-mortem: massive intra-cranial haemorrhage was found.

In the 7th case, delivered by Caesarean section at 32 weeks on account of severe pre-eclampsia, the infant made ineffective gasps for almost 2 hours before it died. Unfortunately no post-mortem examination was made in this case. In the 8th case the mature infant was delivered by forceps after labour for forty hours. The foetal heart was beating strongly and spasmodic gasps were made and continued for nearly three hours before the infant finally died. In this case post-mortem examination failed to show any obvious cause for death, but certainly the stress of labour had been severe and there was possibly a traumatic factor. This is the only case in the series of a mature infant without maternal or obvious foetal pathology, which failed to establish regular breathing. On the basis of these results, it seems clear that mature and undamaged infants will be able to inaugurate breathing successfully without active interference. Failure to establish respiration, in a mature foetus, may be accepted as a sign of serious birth trauma, and such a condition in an undamaged infant is so rare that the possibility can be ignored. The scope of resuscitation procedures (by oxygenation, etc.) in mature infants is clearly very limited.

(2) *Relation between the duration of foetal apnoea and neonatal death.* From a study of hospital records, it should be possible to establish the existence, and to analyze the degree, of any association between the duration of foetal apnoea and foetal death. The situation is slightly different in mature and in premature infants, and the case of mature infants may be

TABLE IV

Caesarean Sections in Selected Mature Infants, 1946–1956

Period of Apnoea	Satisfactory Under 5 minutes	Fair 5–10 minutes	Long 10–20 minutes	Very long Over 20 minutes
403 elective sections:				
Alive	308	63	29	2
Died	1	—	1	—
238 emergency sections:				
Alive	96	44	71	28
Died	1	—	—	—

considered first. After normal vaginal delivery, I find records of prolonged apnoea are so rare that I have not been able to make a satisfactory table, while the use of forceps introduces confusion from the risk of foetal trauma. I have found it best to use, for this analysis, the series of records of infants delivered by Caesarean section. In practice it is in these cases that the call for resuscitation arises most often. Table IV is based upon Labour Ward notes. A report upon the condition of the infant at delivery, and for a little time after, is recorded by the labour ward Sister in charge of the baby. As a rule the time of onset of normal respiration is noted accurately, and the table has been made without difficulty from these records. Details are not complete in a few cases which are omitted from the table. Four grades of apnoea are defined and I have given separate tables for elective and for emergency operations. Almost all sections for pre-eclampsia are recorded as elective operations.

Table IV shows first-week deaths only, omitting multiple births, stillbirths, lethal abnormality and disease (Rh affected infants, etc.) and cases with A.P.H. It is noticeable that infants delivered with A.P.H. due to placenta praevia and to abruptio placentae, commonly show impaired vitality and not rarely fail to establish respiration. Such cases have not been included in this table, since the outlook for the infant is already impaired. The emergency series is made up of cases with slow advance or of definite obstruction in labour. In nearly all cases the operations were performed under general anaesthesia. The influence of prolonged and difficult labour upon the condition of the foetus and the common sequel of prolonged apnoea, is clearly emphasized in the table. At the same time it is apparent that the tolerance of the newly-born to post-partum apnoea is truly remarkable, and many striking cases are included in the last group, in which regular breathing was not established for over 20 minutes. The following example may be given:

Para-4, aged 36. Emergency admission at term, obstructed after many hours of labour. Delivered by Caesarean section. The infant of 8 pounds 1 ounce was much distressed and cyanosed, but after giving occasional gasps for 2 hours it recovered rather suddenly and breathing became normal. After this the infant did not give any trouble and left the hospital with its mother on the 15th day.

These figures show, in a striking manner, that in mature infants the duration of apnoea does not appear to have any marked influence upon survival, and it seems unlikely that the newborn infant is as sensitive to the effects of anoxia as many workers believe. The commonly repeated statement that oxygen is the most pressing need of the apnoeic infant is not endorsed by these findings. While low blood-oxygen figures following delivery by Caesarean section have been reported by many workers, the significance of this observation appears to need more investigation. Neither does it seem possible that the newly-delivered foetus is in the position of an adult individual in anoxic apnoea (Eastman and Kreisselman, 1941) as has been suggested. In the newly-born but apnoeic infant a functional respiratory centre is certainly present and will remain sufficiently active to inaugurate normal breathing when the proper

moment arrives. This centre does not need "reviving" by extra-pulmonary oxygen nor by any other ancillary procedure. It is possible that in most cases in which the onset of regular breathing is delayed, respiratory movements are made during the phase of apparent apnoea, but such movements are so slight that they escape detection. These observations are completely endorsed by the findings of Henderson, Mosher and Bittrich (1957) recently published. These authors report numerous estimations of blood-oxygen made upon infants born under a variety of conditions, including Caesarean section. No constant relationship could be shown between the oxygen saturation and the survival or condition of the infants at birth, but the serious implications of ante-partum haemorrhage were recorded. The authors concluded that "the oxygen capacity and oxygen saturation in the newborn are not the most important factors in survival . . .".

When considering the results of delivery by Caesarean section a note on the anaesthetic techniques employed is necessary. Many different anaesthetists were concerned in the series, and a variety of methods were used, but two officially appointed, Dr. Isobell Mitchell and Dr. Norman Stott, were responsible for just under 80 per cent of the total. Unfortunately no attempt was made to introduce controlled conditions and detailed analysis of the anaesthetic results is not possible. The following rough analysis will give some indication of the methods employed by the official anaesthetists.

1943. Nitrous-oxide-ether-oxygen sequence.

1944–1947. Induction by pentothal used for a trial series of 100 cases. The results were not considered satisfactory and other experiments were made, followed by a return to induction with nitrous-oxide followed by ether-chloroform mixture. The rather frequent delivery of frothy (mucousy) infants was thought to be related to the use of nitrous-oxide for induction, and this was gradually dropped.

1948–1956. Induction by chloroform-ether mixture on an open mask, followed by C+O+E mixture until the infant was delivered. This has been the standard method during this period, and it has been used by the two regular anaesthetists for 607 cases. It has proved satisfactory, safe in cases of obstructed labour, and the open mask is thought to reduce the risk of causing maternal anoxia during induction. Premature infants have died with the pulmonary syndrome following every method employed, including delivery under local anaesthesia. Although no formal analysis is attempted, all case records have been examined. It is difficult to suggest that any one of the techniques used has been associated with increased neonatal mortality or with increased duration of foetal apnoea. No doubt a general anaesthetic is often responsible for some delay in the commencement of breathing, but this effect appears to be variable and unpredictable.

In the case of prematures many factors of pregnancy and labour have to be considered, and in all cases the infant's chance of survival

TABLE V

Survival of Small Prematures, 1949–1956

Weight	2·1–3 pounds	3·1–4 pounds	4·1–5 pounds	Died Per cent
Vaginal delivery. Condition satisfactory:				
Total	17	68	197	
Died	11	8	8	9·5
Vaginal delivery. Condition not satisfactory:				
Total	14	19	24	
Died	12	8	2	38·6
Caesarean section. Condition satisfactory:				
Total	9	21	29	
Died	6	8	2	27
Caesarean section. Condition not satisfactory:				
Total	10	12	16	
Died	6	1	6	34

is already prejudiced, since by definition abnormal features are certainly present. In view of these difficulties precise analysis of this series is not attempted, and in Table V I have simply shown the rate of survival when the cases are placed in two categories: (1) satisfactory at birth, when the infant appears to be in good condition and regular breathing is established in five minutes or less; (2) unsatisfactory, when the infant is not in good condition and regular breathing is not established or occurs later than five minutes after birth. This table includes all prematures (including twins) up to 5 pounds in weight, delivered in the hospital in the years 1949–1956 inclusive. Deliveries by Caesarean section and vaginal deliveries are tabled separately.

In this series there is no attempt to make any distinction between different causes for neonatal death, nor to explain the reason for prematurity. While the "condition" at birth is evidently of great importance, it appears to me that the table emphasizes another feature that is more surprising. This is the high proportion of neonatal deaths that occur in small prematures following apparently satisfactory recovery after birth, with rapid establishment of normal breathing, often with vigorous cry and movement. Of the 78 infants who failed to survive, 43 (55 per cent) were considered to be in good condition at birth and in these normal respiration appeared to be established. In a few cases there was some explanation for the death of the infant, but in many more death followed the development of the pulmonary syndrome. I find it difficult to suppose that an infant who is already breathing can be helped by any resuscitation procedure, and no assistance should be required unless some essential preliminary adjustment has failed to make the lungs efficient. While anoxia must follow any embarrassment of respiration, it seems natural to look elsewhere for the basic cause of death.

Discussion

The problems presented by the apnoeic baby have always aroused much interest. Treatment of some kind seems urgently necessary and during my experience I have witnessed many changes of fashion, each method in its day believed to be life-saving, but without acceptable proof. The great difficulty facing therapeutic practice has been always ignorance of the physiological changes that occur during the transition from foetus to infant, i.e., at the commencement of extra-uterine life. Perhaps no single happening at this moment is of greater importance and at the same time shrouded in so much mystery, as the establishment of respiration, which at first sight seems such an obvious procedure that an explanation is scarcely required. The serious lack of basic knowledge concerning this function has been emphasized lately by the findings of the Special Committee on Infant Mortality of the New York Medical Society in their Symposium (Abramson, 1956) on the Resuscitation of New-born Infants. In fact it is still doubtful whether the stimulus that prompts the first inspiration is understood, and the mechanism that effects inflation of the lungs is obscure, although certainly far more complicated than was supposed a few years ago. With this background of uncertainty constant efforts are needed to assess the value of the measures for resuscitation of infants that are employed today, some of which may be potentially harmful. With this end in view, I believe that comparison with the clinical results of the series analyzed above may be of value.

All procedures for active resuscitation such as tracheal catheterization, rocking and automatic breathing machines, must involve some disturbance of the infant. Intra-gastric oxygen insufflation, which is now used so widely, involves less handling of the infant, but estimates of the value of this procedure are chiefly based upon clinical impressions and proof of benefit is wanting. It seems quite possible that too much attention is concentrated upon the correction of anoxia in the minutes after birth, and other factors, for example a circulatory adjustment, may be of greater importance. Perhaps a restful period with complete absence of disturbance, may be important to the foetus during the transition to established extra-uterine existence. The realization of this possibility and increasing confidence in neonatal tolerance of anoxia, led finally to the adoption of the expectant policy which made possible the collection of the series

analyzed in this paper. The results of this clinical trial have been satisfactory. I have not been able to show any disadvantage by comparison with the results of other hospitals which have published similar analyses, even where it is known that active resuscitation is frequently practised. In my view these findings suggest that much of the treatment commonly advised for infants during the immediate post-partum period, is unnecessary. Only in the single group of small prematures which die with the pulmonary syndrome does there appear to be any real scope for active treatment, but there is not any information to indicate whether postnatal resuscitation is helpful in preventing the development of this condition.

When all these points are considered, I feel that it is possible to come to certain conclusions about the behaviour of apnoeic infants treated expectantly, as follows:

(1) In the absence of active post-partum resuscitation procedures, there is not any significant increase in infant loss.

(2) Mature undamaged infants will commence to breathe spontaneously.

(3) The length of the post-partum apnoeic phase does not show any constant relationship with neonatal loss.

In conclusion, I wish to express my grateful thanks to many practitioners who have co-operated with me since 1943 in the management of these patients, and in particular to Trevor Baynes, Esq., F.R.C.S., and to W. B. Smellie, Esq., F.R.C.S.E., who have allowed me to include their personal cases in this review. I owe a special debt to Dr. V. Mary Crosse, *O.B.E.*, for reading and criticizing an early draft of this paper.

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IN VITRO STUDIES OF THE MOTILITY OF THE HUMAN UTERUS

Part III—The Effects of Adrenaline, Noradrenaline and Acetylcholine on the Spontaneous Motility in Different Parts of the Pregnant and Non-pregnant Uterus

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THE spontaneous motility in different parts of the non-pregnant uterus was described in Part I (Sandberg *et al.*, 1957) and of the pregnant uterus in Part II (Sandberg *et al.*, 1958) of this investigation.

These studies were the fundamental basis for the present and the following investigations of pharmacological effects.

MATERIAL AND METHODS

Material. The muscle strips were taken from 155 uteri at hysterectomies and 49 uteri at Caesarean sections. The strips were cut longitudinally and transversely from the following locations: (1) corpus and (2) isthmus (non-pregnant uterus); (1) corpus and (2) lower segment (pregnant uterus). The strips were immediately immersed in Ringer solution. The classification of the non-pregnant uteri was based on the case history correlated with a microscopical examination of the cyclic phase of the endometrium.

Motility. As soon as possible the muscle strips, measuring about 20×2×2 mm., were immersed in an organ-bath kept at 37·5° C., containing Tyrode solution, modified according to Genell (1937)* and oxygenated by a gas-mixture containing 95 per cent O_2 and 5 per cent CO_2. The pH of the oxygenated solution was 7·2. After a period of adaptation of 1–1½ hours the spontaneous motility was recorded isotonically with optimal load for half an hour. Afterwards the drugs were added for about 20 minutes. After washing, the spontaneous motility was recorded for about 20 minutes before a subsequent addition of drug.

The spontaneous motility usually permitted repeated tests for about 5 hours.

The volume of the organ-bath was 20 ml. Acetylcholine was given as chloride, adrenaline

* NaCl 8·0 g.; KCl 0·42 g.; $CaCl_2$ 0·24 g.; $MgCl_2$ 0·005 g.; $NaHCO_3$ 1·0 g.; glucose 0·5 g.; distilled water to 1,000 ml.

as hydrochloride and noradrenaline as bitartrate. The dose given is referred to the amount of base.

Estimation of Effects. The following factors were considered:

(1) Incidence of response.

(2) Change of motility pattern.

(3) Tonus.

(4) Frequency.

(5) Amplitude.

(6) Amplitude maximum.

The estimation was made as follows:

(1) *Incidence of response.* The number of responses (reactors) as percentage of the total number of doses administered (reactors and non-reactors).

The non-reactors were excluded and the following factors are calculated as percentages of the reactors.

(2) *Change of motility pattern.* Change from one type of motility to another following the addition of drug.

(3) *Tonus.* Variation of baseline (a line drawn through the amplitude minima). The positive variation was estimated as +, ++, and +++, corresponding to an increase in tonus of less than 50 per cent, 50–100 per cent and more than 100 per cent of the height of the original amplitude, respectively.

The negative variation was defined in a corresponding manner (Fig. 1).

(4) *Frequency.* Variation in number of contractions per minute. The positive variation was estimated as +, ++, and +++, corresponding

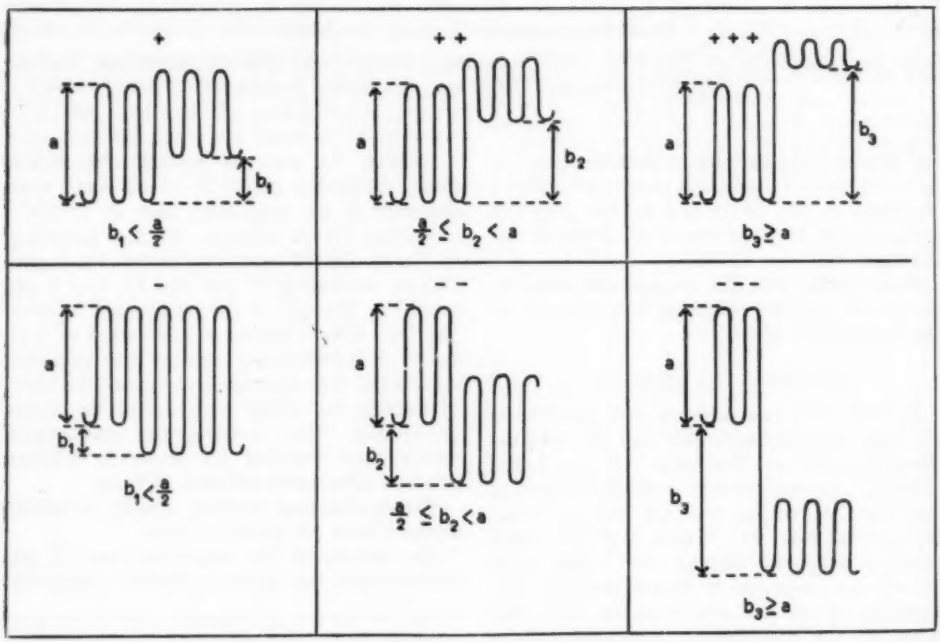

FIG. 1

Estimation of the variation of tonus. For explanation: see text.

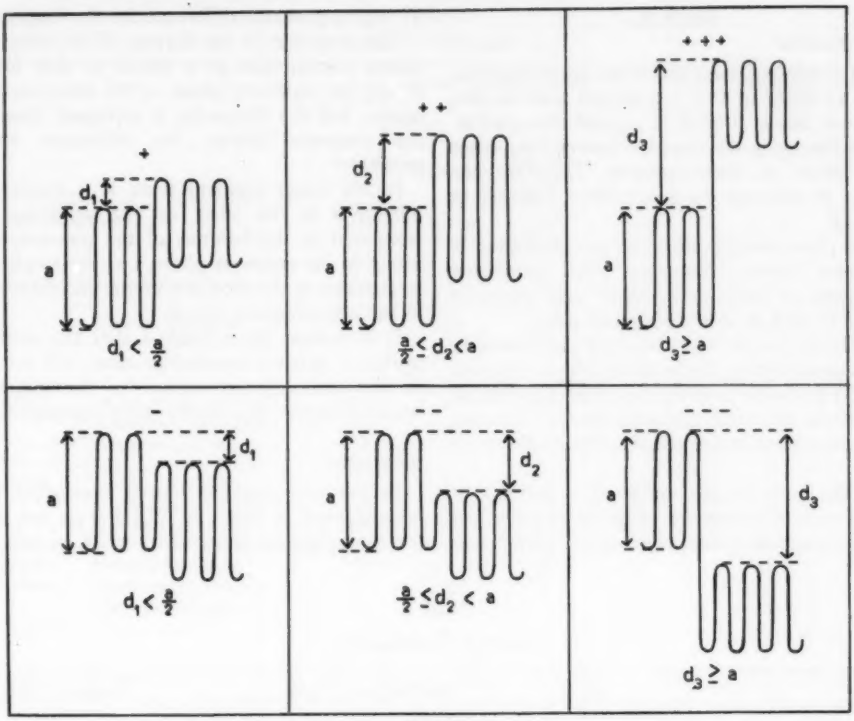

FIG. 2

Estimation of the variation of amplitude maximum. For explanation: see text.

to an increase of less than 100 per cent, 100–200 per cent, more than 200 per cent of the original frequency of contractions, respectively.

The negative variation was defined in a corresponding manner.

(5) *Amplitude*. Variation in height of the contractions. The positive variation was estimated as +, ++, and +++, corresponding to an increase of less than 50 per cent, 50–100 per cent and more than 100 per cent of the original amplitude, respectively.

The negative variation was defined in a corresponding manner.

(6) *Amplitude maximum*. Variation of topline (a line drawn through the amplitude maxima). The positive variation was estimated as +, ++, and +++, corresponding to an increase in topline of less than 50 per cent, 50–100 per cent and more than 100 per cent of the original amplitude (Fig. 2).

The negative variation was defined in a corresponding manner.

This parameter has been used, since it gives a more accurate estimate of the pharmacological response than the amplitude alone, especially in those cases where a small dose of a drug produces an increase in amplitude and a larger dose gives a decrease in amplitude due to a simultaneous elevation of the baseline.

Unless otherwise noticed, the comparisons and statistical analyses (Student's t-test) were carried out on the figures for the increase in the different factors. The significance is graduated as probable ($P<0{\cdot}05$), highly probable ($P<0{\cdot}01$) and significant ($P<0{\cdot}001$).

Results

Noradrenaline

In the non-pregnant uterus noradrenaline was given in doses of 0·5–1·0 μg./ml. and for the pregnant uterus 0·01–0·50 μg./ml. No qualitative difference in the response between the doses used could be demonstrated. Therefore the results of different doses are listed together in Table I.

The characteristic effect of noradrenaline is increased tonus, frequency and amplitude maximum in both proliferative and secretory phases as well as in the pregnant uterus.

In the corpus the sensitivity for noradrenaline is increased during the secretory phase. There is a highly probable difference as regards incidence of response and tonus and a significant difference in the frequency as compared to the proliferative phase.

In the isthmus the increased sensitivity to noradrenaline during the secretory phase is less pronounced than in the corpus and is only shown by highly probable difference for the frequency.

The response in the corpus of the pregnant uterus corresponds as a whole to that found during the secretory phase of the non-pregnant uterus, but the frequency is increased more in the pregnant uterus, the difference being probable.

In the lower segment there is a qualitative difference in the effect on the amplitude as compared to the isthmus of the non-pregnant uterus in the secretory phase, i.e., the amplitude is increased in the pregnant uterus and decreased in the non-pregnant organ.

It is evident from Table I that the isthmus shows a greater sensitivity than the corpus in the non-pregnant uterus. In the pregnant uterus, however, this tendency is less pronounced.

Adrenaline

In the non-pregnant uterus adrenaline was administered in doses of 0·5–1·0 μg./ml. and for the pregnant uterus 0·02–0·50 μg./ml. No

Table I

Effect of Noradrenaline

		Non-Pregnant Uterus				Pregnant Uterus	
		Corpus		Isthmus			
		Proliferative	Secretory	Proliferative	Secretory	Corpus	Lower Segment
Incidence of response		25/35 71%	39/42 93%	39/47 83%	41/43 95%	26/27 96%	72/80 90%
Change of motility pattern (per cent)		36	44	49	61	35	67
Tonus	Increase (per cent)	60	87	74	88	88	85
	Unchanged (per cent)	32	13	26	12	8	15
	Decrease (per cent)	8	0	0	0	4	0
Frequency	Increase (per cent)	48	80	74	96	96	95
	Unchanged (per cent)	40	20	23	2	4	5
	Decrease (per cent)	12	0	3	2	0	0
Amplitude	Increase (per cent)	28	8	33	24	23	65
	Unchanged (per cent)	32	18	41	20	19	14
	Decrease (per cent)	40	74	26	56	58	21
Amplitude Maximum	Increase (per cent)	52	49	69	71	65	87
	Unchanged (per cent)	36	46	31	29	31	10
	Decrease (per cent)	12	5	0	0	0	3

TABLE II
Effect of Adrenaline

		Non-Pregnant Uterus				Pregnant Uterus	
		Corpus		Isthmus			
		Proliferative	Secretory	Proliferative	Secretory	Corpus	Lower Segment
Incidence of response		36/47 77%	46/54 85%	60/62 97%	49/49 100%	63/64 99%	104/106 98%
Change of motility pattern (per cent) ..		33	39	83	82	65	78
Tonus	Increase (per cent) ..	72	80	93	100	84	84
	Unchanged (per cent) ..	17	11	7	0	3	10
	Decrease (per cent) ..	11	9	0	0	13	6
Frequency	Increase (per cent) ..	61	65	91	82	89	90
	Unchanged (per cent) ..	31	28	7	18	1	5
	Decrease (per cent) ..	8	7	2	0	10	5
Amplitude	Increase (per cent) ..	11	9	27	25	27	55
	Unchanged (per cent) ..	14	15	8	14	6	9
	Decrease (per cent) ..	75	76	65	61	67	36
Amplitude Maximum	Increase (per cent) ..	50	55	73	81	73	81
	Unchanged (per cent) ..	31	30	25	14	13	12
	Decrease (per cent) ..	19	15	2	5	14	7

qualitative difference in response to the various doses used was found. Therefore the results of different doses are listed together in Table II.

The characteristic general effect is increased tonus, frequency and amplitude maximum in both proliferative and secretory phases and in the pregnant uterus.

No difference in sensitivity between proliferative and secretory phases was found either in the corpus or in the isthmus.

The pregnant corpus is more sensitive to adrenaline than the non-pregnant corpus in the secretory phase, the differences being highly probable as regards incidence of response, change of motility pattern, frequency and amplitude maximum.

In the lower segment there is a qualitative difference in the effect on the amplitude as compared to the non-pregnant isthmus, i.e., the amplitude is increased in the pregnant uterus and decreased in the non-pregnant uterus.

In the non-pregnant uterus the region of the isthmus is more sensitive to adrenaline than the corpus, the differences being highly probable for the incidence of response, tonus, frequency and amplitude maximum, both in the proliferative and secretory phases. In the pregnant uterus, however, this tendency is less pronounced.

Acetylcholine

In the non-pregnant uterus acetylcholine was given in doses of 0·5–1·0 μg./ml. and for the pregnant uterus 0·5–2·5 μg./ml. No qualitative difference in response to the various doses was found. Therefore the results of different doses are listed together in Table III.

The characteristic effect on the non-pregnant uterus is increased tonus and frequency and decreased amplitude irrespective of the sexual phase.

In the non-pregnant isthmus there seems to be some difference in response between the proliferative and secretory phases. Thus, the sensitivity is decreased in the secretory phase as demonstrated by the change of motility pattern, tonus and frequency, the difference

TABLE III

Effect of Acetylcholine

		Non-Pregnant Uterus				Pregnant Uterus	
		Corpus		Isthmus			
		Proliferative	Secretory	Proliferative	Secretory	Corpus	Lower Segment
Incidence of response		35/38 92%	36/39 92%	51/58 88%	31/35 89%	30/40 75%	28/69 41%
Change of motility pattern (per cent) ..		40	39	55	19	20	21
Tonus	Increase (per cent) ..	86	89	77	68	73	25
	Unchanged (per cent) ..	14	8	23	32	27	75
	Decrease (per cent) ..	0	3	0	0	0	0
Frequency	Increase (per cent) ..	80	92	74	58	60	39
	Unchanged (per cent) ..	11	0	16	26	23	25
	Decrease (per cent) ..	9	8	10	16	17	36
Amplitude	Increase (per cent) ..	3	20	16	16	10	32
	Unchanged (per cent) ..	17	22	27	36	53	61
	Decrease (per cent) ..	80	58	57	48	37	7
Amplitude Maximum	Increase (per cent) ..	57	53	45	48	50	46
	Unchanged (per cent) ..	40	36	49	39	50	50
	Decrease (per cent) ..	3	11	6	13	0	4

being significant, however, only for change of motility pattern.

In the non-pregnant corpus the amplitude is more decreased in the proliferative phase than in the secretory phase ($P<0{\cdot}05$). As regards the tonus all reactors except eight showed increased tonus after acetylcholine. All these eight cases with unchanged tonus were found in uteri from the 19th–25th day of the menstrual cycle.

The pregnant uterus is generally less sensitive to acetylcholine than the non-pregnant uterus, and this difference is most pronounced in the lower segment. There is a significant difference in response between the pregnant and non-pregnant lower segment.

As regards the tonus there is a significant difference between the pregnant lower segment and the non-pregnant isthmus, both in the proliferative and secretory phases. As regards the frequency no difference can be demonstrated between the pregnant lower segment and the non-pregnant isthmus in the secretory phase, but the pregnant lower segment is less sensitive than the non-pregnant isthmus in the proliferative phase ($P<0{\cdot}01$).

A comparison between the pregnant and non-pregnant corpus in the secretory phase shows a decreased sensitivity of the pregnant corpus, the difference in the incidence of response being probable. As regards frequency the difference between the pregnant corpus and the non-pregnant corpus in the secretory phase is significant.

When the effects of acetylcholine on the corpus and isthmus are compared in the non-pregnant uterus, the following facts are observed: In the proliferative phase the amplitude is more decreased in the corpus than in the isthmus ($P<0{\cdot}01$). In the secretory phase an increased sensitivity of the corpus is observed concerning tonus ($P<0{\cdot}05$) and frequency ($P<0{\cdot}01$).

In the pregnant uterus the corpus is also more sensitive to acetylcholine than the lower segment, the difference being significant for the incidence of response and tonus.

FIG. 3

Non-pregnant corpus in the proliferatory phase (9th day). Positive response to acetylcholine and no response to noradrenaline.

FIG. 4

Non-pregnant corpus in the secretory phase (20th day). Positive response to noradrenaline and no response to acetylcholine.

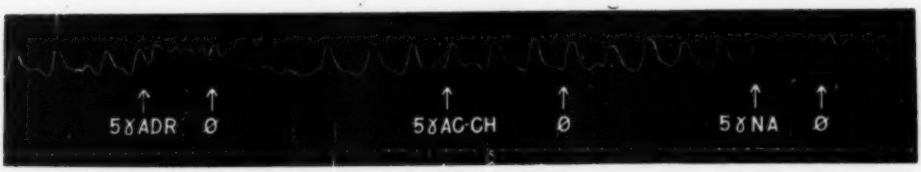

FIG. 5

Pregnant corpus at term. Positive response to adrenaline and noradrenaline and no response to acetylcholine.

FIG. 6

Pregnant lower segment at term. Positive response to noradrenaline and no response to acetylcholine.

F.S., A.I.-S., L.L., G.R. [970]

Discussion

Previous investigations concerning the effect of noradrenaline, adrenaline and acetylcholine on the human uterus *in vitro* have been performed only on limited material. The responses have generally been interpreted without sufficient consideration of the origin of the strips, the sexual phases, the different qualities of the responses and without statistical analysis of the results.

In the present paper, however, these questions have been considered as far as possible.

Since the motility pattern differs in the corpus and in the region of the isthmus—especially the common lack of spontaneous motility in the region of the isthmus—the change of motility pattern and amplitude are not considered in the comparison between corpus and isthmus.

We have been able to confirm the observations of Gunn and Russell (1946) (adrenaline) and D'Incerti Bonini and Confalonieri (1951) (acetylcholine) that the corpus and isthmus of the same uterus may respond in a different manner to the same drug.

Our observations that there is no difference in the sensitivity to adrenaline between proliferative and secretory phases are in accordance with those published by Adair and Haugen (1939). We have, however, found a difference in the sensitivity between the pregnant and non-pregnant corpus, the pregnant corpus being more sensitive to adrenaline. In the isthmus and lower segment no such difference could be demonstrated.

When comparing adrenaline and noradrenaline, the characteristic effects found are increased tonus and frequency in all parts of the pregnant and non-pregnant uterus, thus confirming the results of Garrett (1955).

The isthmus of the non-pregnant uterus is more sensitive to adrenaline and noradrenaline than the corpus. A further common feature in the response to noradrenaline and adrenaline is increased amplitude of the lower segment in the pregnant uterus.

There is, however, a difference between noradrenaline and adrenaline, which is reflected in the increased sensitivity to noradrenaline during the secretory phase; this difference between the phases is not found for adrenaline.

We have not been able to confirm the observation by Garrett (1955) that the uterus is more sensitive to noradrenaline than to adrenaline. This might be explained by the fact that Garrett used Ringer-Locke solution in the organ-bath.

This explanation is supported by the fact that the ED_{50}-values found by Garrett for adrenaline and noradrenaline are roughly 4 and 2 times higher, respectively, than the figures calculated from our material.

A comparison between the response of the uterus to acetylcholine and noradrenaline showed the following differences.

In the proliferative phase the corpus is more sensitive to acetylcholine than to noradrenaline, probable differences being found for the incidence of response, tonus and frequency. In the isthmus no difference in sensitivity to noradrenaline and acetylcholine could be demonstrated.

In the secretory phase the corpus showed the same sensitivity to noradrenaline and acetylcholine. In the isthmus, however, there was a pronounced increase in sensitivity to noradrenaline as compared to acetylcholine, shown by significant differences for the change of motility pattern and frequency, and probable differences for tonus and amplitude maximum.

The increased sensitivity to noradrenaline found in the secretory phase is still more pronounced in the pregnant uterus, especially in the lower segment. This fact is demonstrated by significant differences for all factors tested.

Some characteristic responses to acetylcholine and noradrenaline in the proliferative and secretory phases and during pregnancy are shown in Figures 3–6.

Miller, Cockrill and Kurzrok (1937) studied the effect of acetylcholine on the non-pregnant uterus, using about 500 times larger doses than we used. Therefore, their results are not comparable with ours. D'Incerti Bonini and Confalonieri (1951), in a study on one pregnant uterus, found an increased sensitivity of the corpus as compared to the lower segment, using the same doses of acetylcholine as in this investigation. Our findings are in accordance with those described in their single experiment.

We have also been able to show a decreased sensitivity of the uterus to acetylcholine in the

secretory phase and during pregnancy, most pronounced in the isthmus. This observation might be explained by the findings of Zeller *et al.* (1941), showing that the amount of circulating choline esterase is influenced by the blood level of oestrogens.

This result is also supported by experiments in animals. Sauer, Jett-Jackson and Reynolds (1935) investigated the effect of pilocarpine on the rabbit uterus *in situ*, from castrates, castrates given oestrogen and pseudo-pregnant uteri. Only castrates given oestrogen responded to pilocarpine, showing an increased sensitivity to para sympathetic stimuli during the proliferative phase.

Persianinov (1952), in experiments performed *in situ* and *in vitro* on rabbits and rats, demonstrated that oestrogens increased the sensitivity of uterine musculature to acetylcholine.

Summary and Conclusions

When pharmacological effects are studied on uterine muscle strips *in vitro*, the different response of the corpus and isthmus regions must be taken into consideration. Therefore the strips used must be strictly defined to their anatomical localization in the uterus.

The effects of adrenaline, noradrenaline and acetylcholine on pregnant and non-pregnant human uterus have been studied *in vitro* using a modified Magnus-Kehrer technique.

The pharmacological effects were analyzed and the results treated statistically using the t-test.

The corpus and isthmus were found to respond in a different manner to the same stimulus.

The response varied during proliferative and secretory phases and pregnancy.

The characteristic general effect of noradrenaline is increased tonus, frequency and amplitude maximum.

The sensitivity to noradrenaline is increased during the secretory phase and during pregnancy at term. The isthmus shows a greater sensitivity than the corpus throughout.

The effects of adrenaline are the same as those found for noradrenaline with the exception that no difference in sensitivity between proliferative and secretory phases is found.

The characteristic effect of acetylcholine is increased tonus and frequency and decreased amplitude. The sensitivity of the uterus to acetylcholine is somewhat decreased during the secretory phase and most markedly decreased during pregnancy at term.

A comparison between noradrenaline and acetylcholine shows that in the proliferative phase the corpus is more sensitive to acetylcholine than to noradrenaline. In the secretory phase the isthmus is more sensitive to noradrenaline than to acetylcholine. The increased sensitivity to noradrenaline found in the secretory phase is still more pronounced in the pregnant uterus, especially in the lower segment.

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ECTOPIA VESICAE AND SPLIT PELVIS

An Account of Pregnancy in a Woman with Treated Ectopia Vesicae and Split Pelvis, Including a Review of the Literature

BY

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THE condition known as "split pelvis", "bassin fendu" of French authors or "Spaltbecken" of the German, where the pubic bones fail to meet one another anteriorly, is part of the deformity known as exstrophy of the bladder or ectopia vesicae. All patients with this congenital deficiency of the lower abdominal wall have some degree of split pelvis, but the bony deficit can occur alone.

Exstrophy of the bladder is a most distressing deformity in which the anterior bladder wall is absent and the posterior bladder wall protrudes as a pink tender fleshy mass in the lower abdomen. Urine dribbles away or spouts from the ureteric orifices, so that the sufferer is constantly wet; smelling of urine he is forced to lead an outdoor life and shuns society, ashamed of his secret misfortune. Happily, this deformity is rare, occurring only twice in 100,000 births according to Neudorfer (1886) or four times in 116,300 births according to Spooner (1905).

In the past, Nature mercifully cut short the sufferings of many of these individuals; Orlow reported in 1903 that only 23 out of 74 children born with this affliction passed the twentieth year of life, the others dying of pyelonephritis and other kidney complications: Mayo in 1919 found that 50 per cent of all persons so affected were dead by the 10th year and 66 per cent were dead by the 20th year.

However, since the introduction of the sulphonamides and streptomycin, more and more of these patients are being successfully treated by uretero-colic anastomosis and are surviving to adult life, so that more pregnant women with this complication are likely to be seen in obstetric practice.

This condition is said to have an unequal sex incidence and a predominance of males has been reported by many writers, as shown below:

Sex Incidence of Ectopia Vesicae

		Male	Female	Doubtful
Braxton Hicks	1877	14	2	4
Gusserow	1879	41	8	
Neudorfer	1886	110	100	
Keith, A.	1908	19	7	
Eberbach and Pierce	1928	14	12	
Randall and Hardwick	1934	110	35	
		308	164	4

but one must remember that the deformity is easier for a woman to conceal and many women prefer to suffer rather than submit to examination.

Moreover, the sex of patients with ectopia vesicae has often been in doubt, as it was in the case reported by Champneys (1877), and has even been misdiagnosed in childhood, as in the cases reported by Litzmann (1872), Graham (1942) and McEachern (1950). Litzmann's patient eventually proved her femininity by bearing a child, as also did the patient reported here, who first went to school as a boy.

For these reasons it is doubtful if the male/female ratio is as high as it would appear

from hospital records; nevertheless, there almost certainly is a predominance of males, for the discrepancy is evident even in Sir Arthur Keith's figures for museum specimens of types 1 and 2: in his classification, type 1 is ectopia vesicae in the male; type 2 is ectopia vesicae in the female; type 3 is ectopia vesicae combined with a fistulous condition of the intestine (where he found the sex incidence to be equal, 7 male and 7 female), and type 4 is epispadias where the lower vesical area and/or the penis are cleft.

In Keith's type 2 specimens the uterus and vagina may be single or double, but in all his specimens of type 3 there was duplication of the genitalia.

Champneys (1877) describes four degrees rather than types of ectopia vesicae.

First degree—this is the lowest or slightest degree of deformity tending to extroversion, where the pubic bones are separated but there is no fissure in the abdominal wall; the weak linea alba forms a hernial pouch containing the bladder (cf. Schickele, 1901).

Second degree—here the bladder is perfect but protrudes through a fissure in the abdominal wall (cf. Waldstein, 1897).

Third degree—this is the full deformity where both the bladder and the abdominal walls are cleft (cf. Bonnet, 1724).

Fourth degree—in the highest or greatest degree of deformity the extroverted bladder is separated into two halves by an opening of the intestine (cf. Davies, 1942).

Even in first degree ectopia vesicae the pubic symphysis is split and the pubic bones are often widely separated: a fibrous inter-pubic band or ligament often replaces the missing bone and unites the pubic rami: the lower ends of the rectus abdominis muscles are divaricated and inserted into the separated bones, so forming a triangular window enclosing the malformed bladder.

The umbilicus is often described as being absent, but is in fact represented by a crescentic area of skin, closely applied to the upper edge of the bladder where the umbilical cord had a velamentous insertion, its vessels diverging before reaching the abdomen at a much lower level than normal. For this reason there is often an associated umbilical hernia.

Other associated deformities which may be present include hydrocephalus, spina bifida, hare lip, cleft palate, imperforate anus, renal and ureteric anomalies, bilateral inguinal hernia, rectal or utero-vaginal prolapse and deformities of the lower limbs such as pes cavus.

In an incomplete type of third degree ectopia, the urachus is patent and urine escapes from the umbilicus; this rare condition may be due to some mechanical obstruction of the urethra and seems to be quite different from true ectopia vesicae which is believed to be due to non-fusion of the lips of the hypogastric part of the primitive streak.

The urethra is usually absent, or lacks an anterior wall, in 3rd and 4th degree ectopia vesicae, so that any attempt at closure of the bladder is doomed to failure, for want of an adequate urethral sphincter mechanism. For this reason bilateral ureteral transplantation is the only practicable method of enabling these unfortunate patients to keep dry. After this operation the bladder may be removed and the abdomen can be closed.

Handfield-Jones and Porritt (1957) state that attempts to reconstruct the bladder in patients with ectopia vesicae have always failed.

The patient reported here was therefore quite unusual, for although she had started life with a true 3rd degree ectopia vesicae, an intact urethra was identified when she was 2 years old and a successful bladder closure was performed at that time. In this way her deformity was decreased to one of 1st degree and she obtained complete control of micturition: thus she was spared the pain which arises from contact of clothing with the ectopic bladder mucosa and the risks of pyelonephritis, ureteral calculi, hydro-ureter, hydronephrosis, and even vesical carcinoma, were markedly reduced.

Case Report

The following is the case report of a patient who attended University College Obstetric Hospital.

She was born in a small hospital in Cumberland in 1934 and believes that an operation was carried out there when she was two weeks old. Unfortunately, no records of her neonatal condition, nor of this early surgery can be traced, but another operation was performed by Mr. A. R. Thompson at the Putney Hospital in 1936 when she was 2½ years old: the following is a copy of the only notes which can be found at that hospital now.

"Born with umbilical hernia and extroversion of bladder. Cleft scrotum and penis. Operation. Bladder closed. Satisfactory. Holds water well, 6 to 8 ounces, 4 to 6 hours. Discharged."

Since this operation she says she has always had complete control of her bladder with no frequency, dysuria nor incontinence.

At first she was correctly supposed to be a girl, then at 3 years of age she was considered to be a boy and was given a new first name. She attended school as a boy until she was 10 years old, when it became obvious that she was a girl, so she was removed and wasted two years at home during re-adjustment to her new life. At 12 years of age she was sent to school as a girl.

Menstruation commenced at 13 years of age and she had a regular and normal four or five day loss every 28 or 29 days until she became pregnant in 1956 at 22 years of age. There was always severe colicky lower abdominal pain on the first day of menstruation which was sometimes so severe as to make her vomit.

After leaving school at 16 years of age she attended a College of Art where she eventually met her husband.

Her mother and father are not related to one another and are in good health. She has two older brothers and two younger sisters who are all well. One other sister died at 2 years of age but she knows nothing of the cause.

Pregnancy—Antenatal Care

She was 22 years old when first seen after 12-weeks amenorrhoea. She was a healthy looking, intelligent woman of short stature and average feminine build, with a normal gait. Her height was 5 feet 0 inches (152 cm.) and she weighed 8 stones 1 pound (58 Kg.). Her breasts were well developed and active with everted nipples: the upper abdomen was normal in appearance, but there was no normally situated umbilicus and the skin of her lower abdomen was scarred over an area about 3 inches wide from the pubic region upwards for about 3 inches.

The symphysis pubis was absent and the blunt ends of the pubic rami could be felt 3¼ inches (8 cm.) apart beneath the skin where they were united by a tough fibrous band (Figs. 1 and 2). The lower ends of the rectus abdominis muscles were widely divaricated and inserted into the ends of the pubic rami, so that a triangular window was formed beneath the scarred area of skin.

When she stood erect, the bladder bulged forward through this window beneath the skin as shown in the photograph taken after childbirth (Fig. 3).

The anterior ends of the labia majora were widely separated, but the vulva was covered by hypertrophic labia minora which were fenestrated and irregularly shaped.

There was no clitoris, but just below the fibrous inter-pubic band was a small bright red polyp, like a urethral caruncle, arising from the edge of a small orifice which was at first taken to be the urethra: behind this, but in front of the introitus, there were two more small orifices side by side in the midline. The polyp and these three orifices were further investigated after delivery.

The vagina admitted two fingers and was normal in length. There was only one cervix and the uterus was the size of a normal 14-week pregnancy. Physical examination was otherwise normal and there was no sugar or albumin in the urine; the blood pressure was 114/65 mm. Hg; chest X-ray, haemoglobin and Wassermann reaction were all normal.

At 20 weeks she began to have bouts of pain in the left iliac fossa but these disappeared spontaneously. At 32 weeks the foetus presented as a flexed breech in the right sacro-anterior position; there was a recurrence of vomiting at this time with some upper abdominal pain, and on one occasion a small haematemesis, but these symptoms were relieved when the foetus turned spontaneously to a vertex presentation at 33 weeks.

By the 34th week her weight gain was 29 pounds and her blood pressure was 130/70 mm. Hg: at this stage of pregnancy the foetal membranes ruptured spontaneously with the escape of clear liquor amnii, and she was admitted to the labour ward.

Labour

On admission to hospital weak irregular uterine contractions were felt. The fundus uteri was 8 cm. below the xiphisternum and the uterus was as broad as it was long. The foetus lay in the left occipito-lateral position and the foetal head could be felt so plainly through the window between the rectus muscles that it gave the impression of an extra-uterine pregnancy. However, vaginal examination confirmed that the pregnancy was intra-uterine for a foetal hand

and the anterior fontanelle were felt through the cervix which was taken up and 2 cm. dilated.

X-ray confirmed this compound presentation but labour was allowed to proceed in the hope that it would correct itself. The foetal heart rate was normal and remained so, while the uterine contractions became stronger and more frequent.

Six hours later the cervix was found to be three fingers (5 cm.) dilated and the right hand had now prolapsed right into the vagina below the head. Strong uterine contractions were coming every three minutes and on abdominal examination the lower segment of the uterus felt very thin and tender on the left side. Caesarean section was seriously contemplated, but as the foetus was small and the pelvis capacious, it was considered that vaginal delivery should be possible.

Nine hours after admission and 16 hours after the premature rupture of the membranes, the umbilical cord suddenly presented at the vulva along with the right hand which now became visible.

Delivery

On vaginal examination the cervix was found to be fully dilated and the head was lying occipito-anterior in front of the sacrum with the right hand and the cord below it. Pending the arrival of an anaesthetist the perineum was infiltrated with 1 per cent xylocaine and a long medio-lateral episiotomy was performed to avoid pressure on the premature foetal skull and also to avoid the possibility of any tearing of the unsupported anterior peri-urethral tissues during delivery. General anaesthesia was then induced (with nitrous oxide, oxygen and di-vinyl ether) about 5 minutes after the cord prolapse had first been noted. The umbilical cord was disentangled from the prolapsed arm, the arm was pushed up and Haig Ferguson's forceps were applied to the head. Gentle traction on the handles of the forceps was combined with firm backward pressure on their shanks, to keep the head well back in the pelvis, so as to avoid damage to the urethra.

At 4.20 a.m. on 6th January, 1957, a normal living male child weighing 5 pounds 7 ounces (2,460 g.) was delivered; the umbilical cord was found to be once round the neck as well as having been once round the arm. An intravenous injection of ergometrine 0·5 mg. was given to the mother as the child's shoulders were delivered and the third stage was soon completed; blood loss was not heavy. The baby was limp and did not gasp for 10 minutes, so intragastric oxygen was administered. Regular respiration was established after 30 minutes.

The episiotomy wound was repaired; there was no damage to the anterior vaginal soft tissues and the fibrous pubic bar was felt to be intact.

The child's right hand was blue and oedematous from having presented throughout labour, but it showed normal movements; its colour improved after a few days and the oedema subsided.

Puerperium

Apart from a mild recurrence of abdominal pain on the 6th day after delivery, for which no cause was found, convalescence was uncomplicated. The temperature never rose above 99° and the uterus involuted normally.

The patient was discharged from hospital, breast feeding the baby, on the 16th day, but lactation failed a few days after she arrived home.

Subsequent Progress and Investigation

When seen 8 weeks after delivery, the patient complained of pain in the left lumbo-sacral region and left iliac fossa, which was initiated by walking but relieved by rest. She also complained of irritation and extreme tenderness of the small anterior vulval polyp which appeared to be inflamed.

The uterus was fully involuted, but was sharply deviated towards the left side of the pelvis, suggesting a uterine anomaly. There was perhaps a little more bulging forward of the bladder in the lower abdomen but no utero-vaginal prolapse had resulted from her labour.

She was re-admitted to hospital a week later but full physical examination failed to reveal the cause of her pain. Her spinal and hip movements were full and painless, and sacro-iliac manipulation did not cause pain.

FIG. 1

X-ray showing absence of symphysis pubis.

FIG. 2

Photograph showing scar of repaired ectopia vesicae and ridge due to ligamentous inter-pubic bar (11 days post-partum).

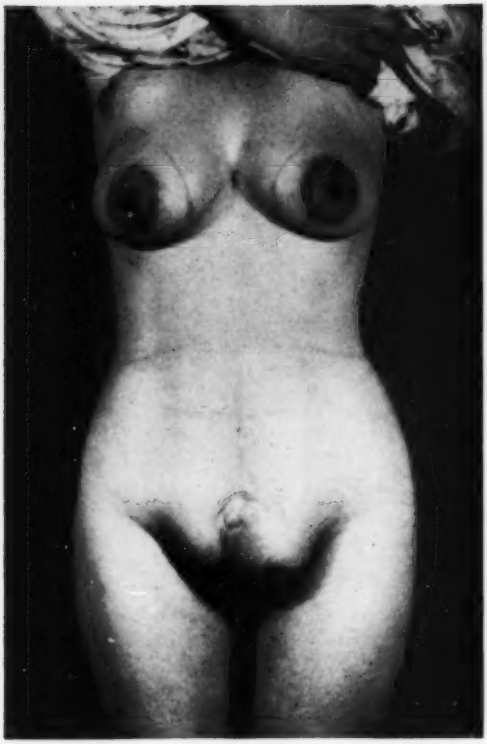

FIG. 3

This photograph of the patient taken 11 days after delivery shows the herniation of the bladder between the divaricated rectus abdominis muscles.

Note the apparent absence of umbilicus, which is actually situated just above the bladder hernia.

FIGURARUM EXPLANATIO.

FIGURA Octava.

A. Epigastrium.
B. Regio umbilicalis.
C. Hypogastrium.
D. Regio pubis.
E E. Spongiosa ossa.
F F. Meatus urinarii, a partu satis visu faciles.
G. Orificium transversale.
H. Oblongum orificium.
II. Cicatrices duæ, ex Urinæ, ut videtur, acrimonia.
K. Anus, paululum anterius locatus.

FIGURA Nona.

P P. Fissura magna quatuor pollices oblonga.
L. Procidentia uteri.
M. Os Tincæ.

FIG. 4

This illustration appeared in the Transactions of the Royal Society, 1724, showing "the preter-natural structure of the pudenda" of a woman delivered by Mr. John Bonnet, Surgeon at Fowey in Cornwall. His account of her difficult labour is the first known record of pregnancy in a woman with ectopia vesicae.

Bonnet in his description of this patient states quite clearly that "there was no sign of an umbilicus", but one is plainly evident in each figure, so these diagrams would seem to be partial modifications of a normal bust.

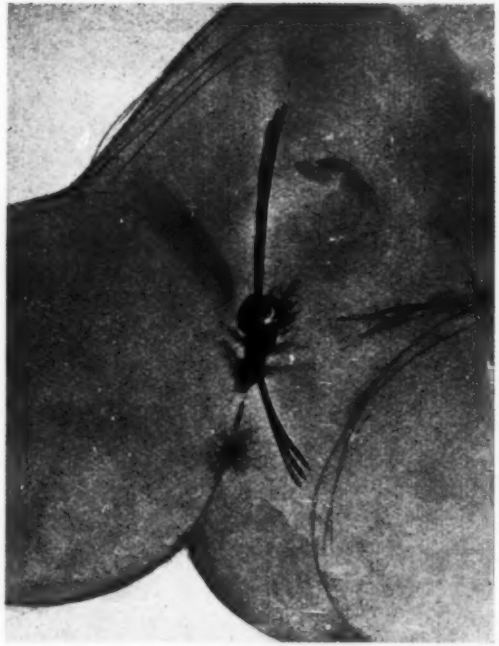

FIG. 5

This drawing of the present patient at 2 years of age in 1936 has been reproduced from A. R. Thompson's article in the *British Medical Journal* of 3rd July, 1937. Salmon gut probes are shown passing through the proximal urethra from the bladder.

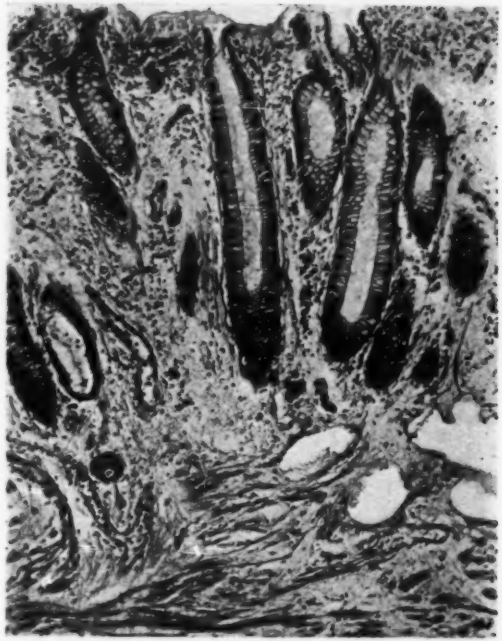

FIG. 6

Photomicrograph of part of a section of the ectopic bladder mucosa which presented as a small bright red polyp in the region where the clitoris would normally be expected. This intestinal type mucosa is typically found throughout the bladder in untreated ectopia vesicae. It does not necessarily imply any bowel involvement in the abnormality as occurs in 4th degree ectopia vesicae. Plain muscle fibres may also be seen in the lower part of the photograph. × 85.

The following investigations were carried out:

(1) *Urological*—voluntary bladder capacity, urine microscopy, blood urea and intravenous pyelogram were all normal.
(2) *Haematological*—haemoglobin, differential white cell count and erythrocyte sedimentation rate were all normal.
(3) *Hysterosalpingogram* showed a normal uterus with filling of both Fallopian tubes.
(4) The sex chromatin of a buccal smear was examined by Dr. P. E. Hughesdon who was given no information as to the origin of the material. He found 61 female and 39 male nuclei in 100 cells and diagnosed the patient's sex as female.

This suggests that a correct diagnosis of sex could have been made in childhood if the method had then been known.

Examination Under Anaesthesia

The uterus was anteverted, mobile and normal in size; both ovaries felt normal. The labia minora were tattered and irregularly fenestrated; the mons pubis was replaced by a scarred area of skin covering a transverse fibrous band which bridged an 8 cm. gap between the pubic rami. About 3 cm. below this bridge was a bright red polypoid structure 1 cm. across, hanging by a broad stalk from the right anterior wall of a blind sinus 2 cm. deep. About 2 cm. posterior to this was what appeared to be a double urethral orifice, the right side of which led upwards and laterally to the bladder, while the left side ended blindly at 1 cm.

The polyp which had at first been mistaken for an urethral caruncle was now seen to arise well in front of the urethra and was thought to be an inflamed clitoris. As it had been nothing but a nuisance to her, it was excised and sent for histological study. Dr. P. E. Hughesdon's report was as follows:

"The polyp is lined partly by squamous epithelium and partly by glands of colonic or rectal type, without a typical mucosa or muscularis. In the centre are some glands of urethral (Skene) type. No evidence of carcinoma. Intestinal type of mucosa is typically found throughout the bladder in untreated ectopia vesicae; it is a change resulting from exposure and is not present at birth."

Cystoscopy (Mr. D. A. Bailey)

A cystoscope was introduced into the bladder through the right side of the double urethral orifice. The bladder accepted 300 ml. of water but was rather irregular in shape, there being a large loculus anteriorly. The right ureteric orifice was identified; its lips were a little oedematous; the efflux was clear and forceful. The left ureteric orifice was situated a little higher in the bladder and was slit-like; the efflux was clear.

The inter-ureteric bar dipped downwards towards the urethral opening.

There was no evidence of cystitis.

Dilatation of the urethra for cystoscopy in no way interfered with her bladder control which was perfect, and although she was troubled by this pain in her side on walking, her general health was good.

Six months after delivery she was not so much troubled by the pain, but seemed very depressed and complained of an increased forward bulging of the bladder; one felt that this could be adequately supported by an elastic "roll on" but she was insistent on having it repaired.

In December, 1957, Mr. D. N. Matthews performed a neat plastic repair of the bladder hernia without opening the bladder; the anterior layer of the rectus sheath was turned in on each side to meet in the midline and this was reinforced by three layers of fascia lata as a free graft.

Previous Report of the Present Patient

This young mother is unaware that she already features in the literature on ectopia vesicae, albeit as a boy, for the late Mr. A. Ralph Thompson described the repair of her bladder in the *British Medical Journal* in 1937, in an article entitled "Vesical extroversion with control of micturition". There is no doubt at all that his Case 1 in that paper is the present patient, for all the details including the year and place of birth, the age at operation, the hospital, the surgeon and the nature of the

lesion agree precisely with the history obtained from the patient. Mr. Thompson was undoubtedly a most astute observer and had an extensive knowledge of ectopia vesicae, for he made a great advance in the treatment of this condition following his discovery of the existence of an intact proximal urethra in several instances.

It seems odd then that such an observant man should have misdiagnosed this patient's sex. He stated "I had no hesitation in pronouncing the child to be a boy". His diagram of her condition at that time does not show any phallus and it seems that his diagnosis of sex was based on the appearance of a painful non-inflammatory swelling in the left groin which he believed to be a testis.

Since the sex of many other children with ectopia vesicae has been misdiagnosed and since the accurate sex diagnosis is now possible by the study of the nuclear chromatin in skin biopsies, buccal smears or blood leucocytes, it is surely wise to investigate all children with ectopia in this way, so that they can be correctly sexed at an early age.

Survey of the Literature

An extensive search of the literature of many countries has disclosed 64 pregnancies in 45 women with varying degrees of ectopia vesicae. These pregnancies included 4 abortions and 1 set of twins, so 61 viable infants were born. There were 2 maternal deaths and 9 stillbirths: three of the liveborn infants died, so only 49 children survived from the 64 pregnancies.

Many difficulties have been encountered by obstetricians in delivering women with this condition.

The first record of pregnancy in a woman with ectopia vesicae is to be found in a letter from Mr. John Bonnet, Surgeon at Fowey in Cornwall, to Claudius Amyand, Serjeant Surgeon to His Majesty, in the *Transactions of the Royal Society*, 1724. Two diagrams were appended, showing the "Preternatural Structure of the Pudenda" of this woman and these are reproduced here with the original legend (Fig. 4). The following extract from his letter shows how difficult was the problem of delivery and how perplexing the dilemma in which he was placed.

"July 18, 1722. I was sent for late at night. I found the woman with true travail-pains upon her. The throws were excessive violent, and the continued agony had almost quite exhausted the poor woman's spirits; but the orifice of the vagina was no way sensibly dilated, tho' the anus, thro' the violence of the throws, opened extremely wide. In vain were all endeavours to relieve her, by thrusting up the child, and putting the mother in a proper posture. Vain were her own throws and agonies. Convulsions now had seized her, and nature seemed to have denied a longer life to the mother, or an entrance into it to the child.

"I was in the utmost perplexity what to do under these circumstances. On the one hand I considered that if there was not a passage made for the child, and that by incision, both mother and child must speedily perish. On the other hand I foresaw the danger and hazard of an incision, and the unavoidable censure of having killed the woman, if she should die under the operation."

He solved this problem by making a vertical incision between two orifices which were present in the pubic region and by dividing the transverse membrane between the two passages to which they led. This done, he introduced his hand, felt the head of the child, thrust a finger in its mouth and drew forth a living well-formed female child.

Unfortunately, the mother developed procidentia and a recto-vaginal fistula. Several other authors have reported vaginal stenosis, resulting in obstructed labour in these women, and extensive bilateral episiotomies or Schuhardt's incisions have often been needed to effect delivery.

Jellet and Madill (1921) in their manual of midwifery stated that little or no difficulty is experienced during labour in women with split pelvis in consequence of the absence of any resistance in front, but personal experience and that of others does not confirm this.

Malpresentation of the foetus is quite common, partly because of the frequency of associated uterine anomalies, but also because the pelvis, when widely split, fails to control the presenting part especially when the foetus is small and premature, which is often the case.

Analysis of records shows that 25 foetuses presented by the vertex, 7 presented by the breech, 5 lay transversely, 2 had a compound presentation and 1 was a shoulder presentation. In 21 the presentation was not recorded. Thus malpresentation occurred 15 times in the 40 cases where the lie of the foetus is recorded, an incidence of 37 per cent.

Even if one assumed that the unrecorded presentations were all normal, there would still be an incidence of malpresentation of 15:61 or 25 per cent.

The methods used to deliver this interesting group of women were bizarre and are difficult to classify, for they include Schuhardt's incisions of the perineum, Dührssen's incision of the cervix, pubiotomy, vaginal Caesarean section, Caesarean laparo-trachelotomy, classical and low classical Caesarean section, as well as the more mundane use of forceps and breech extraction or version and extraction.

Both Bonnet (1724) and Hamilton (1834) delivered their patients by incision of the pubic region, so one does not know whether these should be called abdominal or vaginal deliveries: if they are considered as having been vaginal, then 37 women with ectopia vesicae were delivered *per vaginam*.

Records of the subsequent progress of 34 of them are available and it is a startling fact that 20 developed uterine prolapse. Moreover, there were 2 maternal deaths among these 37 women and of their 52 infants 9 were stillborn; this constitutes a stillbirth rate of 173 per thousand among those delivered vaginally.

Abdominal deliveries included one woman whose pregnancy was terminated by hysterotomy at 28 weeks for pyelonephritis and 7 women delivered by Caesarean section. In this group of 7 women delivered of 8 infants by abdominal section there was no foetal nor maternal mortality and none of them developed uterine prolapse; this is only a small series, but it stands in striking contrast to the results of vaginal delivery.

As regards the relative mortalities in the two groups, one must bear in mind the fact that the abdominal sections were all performed since 1924, while many of the vaginal deliveries occurred earlier.

Further, it must be stated that virginal prolapse does occur in women with ectopia vesicae (Ismail, 1939; Clayton, 1945; Overstreet and Hinman, 1956), so some of the women might have developed prolapse even if they had never been pregnant: in fact, some of these patients were observed to have uterine prolapse during their first pregnancies; nevertheless, there is no doubt that vaginal delivery made the prolapse worse in many women and caused it in others.

Discussion

Many authors have stated that ectopia vesicae does not occur in animals, but there is at least one case on record and that was in a male cat observed by Saint-Hilaire (1832), which also had a split pelvis. Nevertheless, it must be extremely rare.

Sexual intercourse is denied to men afflicted with this condition as a result of the severe degree of epispadias which is usually associated and there appears to be no record of any such man becoming a father.

The condition is rarely met in adult women and few of these were inclined to marry until uretero-colic anastomosis, introduced in 1851 (Simon, 1852) became widely used earlier in this century. The successful surgery of today means that more women with this condition will be reaching adult life and they will want to know the risks of handing on the defect to their offspring. The 64 pregnancies in women with varying degrees of ectopia vesicae reviewed here, produced 61 viable infants, none of whom was recorded as having shown any gross deformity.

Moreover, it seems that the 45 malformed women were all born of normal parents and the only records of familial deformities have been in siblings, suggesting that possibly a combination of two recessive genes may be responsible. One woman with ectopia vesicae reported by Randall and Hardwick (1934) had two brothers who died young with ectopia vesicae: Schickele (1901) reported a woman with ectopia vesicae whose dead sister was said to have had deformed genitalia.

The extreme variety of types and degrees of ectopia vesicae makes it difficult to classify;

some of the 45 patients considered in this review did not have the full deformity, namely "congenital hiatus of the bladder" but they all had some of the characteristic stigmata, such as split pelvis, low umbilicus and cleft, absent or double bladder. Perhaps the real oddities, such as the woman with a split pelvis and duplication of the bladder, uterus, vulva and vagina, described by Gemmell and Paterson (1913) should be included in a separate group with von Engel's (1886) patient; but the fact that the umbilicus was described as being absent makes one suspect that these are all varieties of the same anomaly, known as "ectopia vesicae". The second patient reported by von Franqué (1914) who had a split pelvis and a double uterus and vagina, also had a herniated bladder, so these deformities do seem to be related. This is further supported by James Young's (1958) report of one of two sisters with double uteri, who gave birth to a male child with ectopia vesicae.

Conclusions

Five main obstetric problems have arisen in this group of patients.

Firstly, pyelonephritis which affects untreated cases of 3rd degree ectopia vesicae, also occurs after uretero-colic anastomosis. This can now be treated by specific chemotherapy.

Secondly, premature labour frequently occurs; one might be able to prevent this by strict bed rest after the 28th week of pregnancy.

Thirdly, malpresentation occurs in more than 25 per cent of cases; this may partly be due to prematurity, but is also related to the lack of guidance by a split pelvis; also associated uterine malformations when present may cause malpresentation.

Fourthly, vaginal stenosis has caused obstructed labour and necessitated deep bilateral episiotomies or Schuckardt's incisions in some patients. When vaginal stenosis is severe, Caesarean section would seem preferable to vaginal delivery.

Fifthly, utero-vaginal prolapse has occurred in more than half of the patients delivered vaginally; this is undoubtedly due to a lack of ligamentous support in the split pelvis.

Unfortunately, utero-vaginal prolapse in women with ectopia vesicae is a particularly difficult condition to treat, as has been shown by Overstreet and Hinman (1956). It is therefore important that one should do all one can to avoid prolapse, either by making a generous episiotomy and performing a forceps delivery, pressing backwards firmly on the shanks of the forceps to protect the soft unsupported anterior vaginal tissues, or by Caesarean section.

Dawson (1933) goes so far as to say that all women with ectopia vesicae should be delivered by elective Caesarean section.

No one can question the strong arguments in favour of Dawson's policy and it should be adopted in the majority of patients with this condition, but there may still be patients who can safely be delivered vaginally with constant watchfulness and proper technique.

If the baby in the case reported here had not been small and premature, Caesarean section would have been the best method of delivery.

Summary

Present Patient

The pregnancy and labour of a woman with "split pelvis" is described. She was born with ectopia vesicae, but the bladder had been closed at 2 years of age. She was treated as a boy till 10 years old. Pregnancy was complicated by premature rupture of the membranes. A compound presentation resulted in prolapse of the umbilical cord but a normal living child was delivered with forceps.

Other Patients

A survey of the world literature disclosed 64 pregnancies in 45 women with varying degrees of ectopia vesicae. These pregnancies have resulted in 2 maternal deaths, 49 live births and 9 stillbirths. None of the infants was abnormal.

Pyelonephritis, premature labour, malpresentation, vaginal stenosis and utero-vaginal prolapse are the main obstetric problems in this group of patients.

It is concluded that Caesarean section should normally be used to deliver these women to avoid subsequent prolapse, but a special forceps delivery technique is considered preferable for the premature infants.

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THE PREVENTION OF ECLAMPSIA AND SEVERE PRE-ECLAMPSIA

BY

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AN analysis has been made of nearly 5,000 histories, being those of all the booked patients at The Women's Hospital, Crown Street, Sydney, who were delivered during the 12 months ending 30th June, 1956, together with 35 histories, being those of all the cases of eclampsia which occurred amongst the 48,501 booked patients delivered during the 10 years ending on 30th June, 1956.

Consideration has also been given to the investigation carried out by Woodhill *et al.* (1955) on Australian women at King George Vth Memorial Hospital for Mothers and Babies.

By an exacting regime of antenatal care, which began in 1948 and is still progressing favourably, it has been possible to reduce very greatly the incidence of eclampsia occurring amongst booked patients.

The degree of success is shown in Fig. 1.

FIG. 1
Eclampsia rate at "Crown Street".

It will be noted that not a single case of eclampsia occurred amongst the 7,756 booked patients delivered during the 2 years ending 30th June, 1956.

In achieving this result, we have noted that we now hardly ever see a booked patient with severe pre-eclampsia in the antenatal wards.

HYPOTHESES UPON WHICH THE REGIME WAS INITIATED

In addition to routine antenatal care, the following beliefs are considered to be important.

(1) Antenatal care must begin very early in pregnancy.

(2) Excess weight at the beginning of pregnancy must be reduced. The rate of weight gain and the total gain must be controlled.

(3) Excess weight gain is considered to be due to over-eating and to fluid retention. The former probably predominates in the first half of pregnancy, the latter in the second half.

(4) A high protein diet must be given throughout pregnancy with limitation of carbohydrates and fats according to the weight status of the patient.

(5) Oedema must be regarded as evidence of pre-eclampsia until proved to be due to some other abnormality.

(6) A rise of 10 millimetres of mercury in either the systolic or diastolic blood pressure readings must be regarded as an indication to see the patient again within one week.

TABLE I

The Importance of Early Booking

	Pre-eclampsia	Not Affected	Total	Pre-eclamptic Percentage
Booked after 16th week	169	1,239	1,408	12
Booked before 16th week	219	2,823	3,042	7·2

χ^2=27·91 for one degree of freedom. Highly significant.

(7) Haemoglobin values must be maintained at normal levels.

(8) Albumin in a catheter specimen of urine is a late manifestation of pre-eclampsia.

FACTS ESTABLISHED BY THE REGIME

(1) Booking after the 16th week of pregnancy predisposes to toxaemia, as shown in Table I.

(2) Pre-conceptional obesity predisposes to toxaemia, as shown in Table II.

TABLE II

*Incidence of Toxaemia in Subjects with Pre-conceptional Obesity**

	No. of Cases	Toxaemia†	Percentage
Cases of obesity	31	8	25·8
Other cases	152	18	11·8
Cases with no weight data ..	3	0	
Total	186	26	13·9

* Obesity is defined as plus 2·standard deviations or more above the mean for specific age and height. (Woodhill, 1952.)

† P=0·039.

(3) Patients who develop eclampsia have a statistically significant greater total weight gain than the remainder, as shown in Table III.

(4) The greater the total weight gain and therefore the greater the rate of gain, the higher is the incidence of toxaemia, as shown in Table IV.

(5) The over-all perinatal mortality rate has been decreased when comparing the 2 base years ending on 30th June, 1946 and 1956 respectively, as shown in Table V.

COMMENTS ON THE HYPOTHESES

Early Booking

I have shown that booking before the 16th week decreases the toxaemia rate.

In those early weeks of pregnancy, observations of oedema, blood pressure and urine, show little, if any, variations, but weight is a variable factor.

It would therefore appear to be a reasonable assumption that the advantage gained by early booking lies in the correction of excess initial weight and control of the rate of gain in that early period of pregnancy.

TABLE III

Total Weight Gains in Normal and Toxaemic Pregnancy

	Classification	Number	Mean Gain in Pounds	Standard Deviation in Pounds	Standard Error of the Mean in Pounds
Twelve months ended 30th June, 1956	Normal primiparae	818	17·03	6·48	0·23
	Pre-eclamptic primiparae	108	16·57	9·58	0·96
	Normal multiparae	1,975	16·10	7·27	0·16
	Pre-eclamptic multiparae	111	15·47	9·50	0·95
Eclamptics in 10 years ended 30th June, 1956		28	22·32	2·13	2·01

TABLE IV
The Importance of Weight Control in Pregnancy

Weight Increase	Primiparae			Multiparae		
	Normals	Pre-eclamptics	Percentage	Normals	Pre-eclamptics	Percentage
15–19 pounds	271	24	8·0	579	23	3·8
20–24 pounds	198	22	10	441	21	5·0
25–29 pounds	65	16	20	128	6	5·0
30–34 pounds	4	4	50	12	7	21

As regards column 4, $\chi^2=21·59$ for 3 degrees of freedom.
As regards column 7, $\chi^2=45·16$ for 3 degrees of freedom.

TABLE V
Prematurity and Premature Perinatal Mortality Rates

Year	Premature Births	Other Births	Total Births	Prematurity Rate Per cent	Premature Perinatal Deaths	Perinatal Death Rate Per cent Amongst Premature Births	Overall Premature Perinatal Mortality Rate Per cent
1946	287	3,376	3,663	7·8	84	29·3	2·29
1956	424	3,698	4,122	11·5	73	17·2	1·77

As regards column 5, $\chi^2=14·04$ for one degree of freedom.
As regards column 8, $\chi^2=2·68$ for one degree of freedom.

Weight

The Tables have proved that there is a higher rate of toxaemia when the initial weight is excessive or when there is an excess, in the rate of, or total, gain in weight.

It is logical to believe that correction of those faults will lessen the toxaemia rate.

Diet

We have instituted a high protein balanced diet of sufficient calories to achieve the degree of weight control which we desire.

We believe that a high protein diet, at least two grammes per kilogramme of body weight, aids the maintenance of normal haemoglobin values, protects the liver and provides for the nitrogen storage necessary for the foetus.

Oedema

As macroscopic oedema in pregnancy is abnormal, it is logical to regard this sign as evidence of toxaemia unless any other cause is found.

Blood Pressure

The increase in blood pressure which accompanies toxaemia seldom occurs suddenly; therefore, we regard a small rise as a warning that further rises may occur later on.

Albumin

We believe that advance warning of the advent of albumin in a catheter specimen of urine will be given by observations of weight, oedema and blood pressure.

Comments on the Facts

Table III

Seven of the 35 cases of eclampsia had to be discarded because their out-patient records had been lost.

When preparing this Table, in order to have the weight records comparable over the greater period of pregnancy, I excluded all patients who were booked after the 16th week. Further, I excluded all patients who were delivered before the 36th week. In this latter category I had to exclude only 10 primiparae and 37 multiparae. This left 3,012 cases amongst which there were 219 cases of mild pre-eclampsia. There were no cases of severe pre-eclampsia or of eclampsia in this series.

I was unable to show any difference, statistically important, in the total weight gains of the normal and the pre-eclamptic patients because any excess rate of gain was immediately controlled.

Table V

We agree that there is an increase in the prematurity rate in 1956, but the over-all premature perinatal mortality rate has fallen from 2·29 per cent in 1946, to 1·77 per cent in 1956. This decrease is short of the 5 per cent significance point, but the trend is in the right direction.

Clinical Management of the Regime

Attendances

We try to enforce early, regular, and, in the presence of abnormalities, frequent, attendance at the antenatal departments.

The out-patient card contains a column which shows the date for the next attendance and every effort is made to see that this appointment is kept.

Antenatal Beds

An adequate number of antenatal beds must be provided. At least 1 bed per 115 annual deliveries is necessary to ensure hospitalization for abnormalities.

Diet

As early as possible in the pregnancy patients attend classes for instruction in the principles of a high protein, balanced diet. When necessary, individual instruction is given.

When it is necessary to reduce the diet this is chiefly effected by reducing the quantity of the foods made from, or containing, fat, flour, or sugar. Sometimes skimmed or separated milk is used to replace whole milk.

Weight

When the initial weight is excessive, a reduced diet is prescribed and is maintained until the desired weight level has been reached.

When the initial weight is very excessive, the reduced diet is continued all through the pregnancy.

When the initial weight is normal, but the rate of gain exceeds 2 pounds in the first trimester or 3–4 pounds per week in the second and third trimesters the diet is reduced until the rate of gain has been stabilized.

When it is necessary to reduce the rate of gain in the second half of pregnancy the salt content of the diet is decreased in addition to the calories.

If the desired weight control cannot be effected by the above methods, the patient is admitted to an antenatal bed for "weight control". When this has been achieved and provided there are no other abnormalities, the patient is returned to out-patient care.

Oedema

This complication is treated by a reduction in the sodium content of the diet, and by rest of 1–3 hours duration in the middle of each day.

Failure to improve indicates admission for closer observation.

Blood Pressure

Readings of over 130 systolic and 80 diastolic are regarded as abnormal.

Irrespective of the actual height of the blood pressure a rise of 10 millimetres of mercury in either reading is treated by lessening the sodium in the diet and increasing the amount of rest.

If there has been an additional rise in one week the patient is asked to report again in 3 days. A still further rise on that occasion indicates admission for closer observation and treatment.

Albumin

When albumin is present in a catheter specimen of urine the patient is admitted to an antenatal bed.

Comments of the Management

In a patient whose weight is being reduced or maintained at a constant level we do not hesitate to prescribe amphetamine drugs in doses sufficient to control appetite when this is thought to be necessary.

In this regard our observations support those of Coopersmith (1949), in that the amphetamine drugs in doses sufficient to control appetite have no deleterious effects on hypertension.

Case histories numbered 21,909, 6,812, 4, 15,827, 36,400 and many others, each show a weight loss throughout pregnancy and in every case a healthy baby of good size was born.

Two cases are worthy of especial mention.

Serial No. 34,013 reveals the history of a multiparous patient, aet. 32 years, who began her pregnancy weighing 222 pounds. Nephrolithotomy had been performed since the birth of her last child, 9 years previously. By term this patient weighed only 202 pounds and she was well in every respect. Her baby was healthy and weighed 7¼ pounds at birth.

In contrast, Serial No. 3,143 reveals the history of a primiparous patient, aet. 27 years, who began her pregnancy weighing 235 pounds. By the thirty-fourth week the weight had increased by 29 pounds and signs of toxaemia were evident. Despite admission to hospital and surgical induction this patient died from eclampsia 6 days after the birth of a stillborn foetus.

Observations of weight, oedema, blood pressure and urine have enabled early diagnosis of the onset of toxaemia, but prevention of severe toxaemia has been achieved by the widespread advocation of the necessity to begin antenatal care very early in pregnancy, by the maintenance of a correct diet throughout pregnancy, by the correction of excess initial weight and of any excessive rate of gain, during any period of pregnancy.

Statistics have been published in various medical journals which seem to disprove the beneficial effects of weight control, but in none of these publications has consideration been given to the patient's weight at the beginning of pregnancy, nor to her rate of gain from the earliest weeks right through to the end.

Statistics compiled from the middle of pregnancy onwards or for a certain selected period of pregnancy, regardless of the initial weight, are the only ones so far published with the exception of the work of Woodhill to which reference has already been made.

Physicians reduce obesity in hypertension, diabetes mellitus and many other diseases.

Life insurance statistics reveal that the death rate from many illnesses rises concurrently with the degree of obesity.

If then, such importance is attached to weight in the broader field of medicine, surely a similar importance should be attached to this factor in the specialized field of obstetrics.

Summary

(1) The incidence of eclampsia and severe pre-eclampsia at The Women's Hospital, Crown Street, Sydney, has been greatly reduced.

(2) The hypotheses, facts and management of the regime responsible for this reduction have been stated and commented upon.

(3) Statistical analyses have been given.

(4) The over-all premature perinatal mortality rate has decreased.

Acknowledgments

I wish to record my appreciation of the great help given to me by Dr. H. O. Lancaster in preparing the statistical analyses.

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Appendix

The Women's Hospital (Crown Street)

You May Drink

1½ pints milk per day.
Tea, coffee, water, lemon juice—all without sugar.
Saccharin can be used for sweetening.

You May Eat

Breakfast

2 eggs or 1 large grilled chop.
1 thin slice bread with little butter.
Tea, coffee or milk.

Morning Tea

1 orange.

Lunch

Meat, eggs or cheese.
Vegetables (salad or cooked).
1 thin slice bread with little butter.
1 piece fruit.
Milk.

Dinner

Large serving meat or fish.
Very little gravy or sauce.
1 small boiled potato.
2 vegetables.
1 piece fruit.
½ thin slice bread with little butter.
Tea, coffee or milk.

Supper

Milk or milk coffee.

use very little salt

Do Not Take

Sugar, glucose, Dexsal.
Honey, jam, syrup, sweet spreads.
Sweets, chocolates, cocoa.
Chocolate beverages such as Milo, Ovaltine, Bourn-Vita, Aktavite.
Soft drinks, cordials, milk shakes.
Alcoholic drinks.
Biscuits of any kind (no Saos, Vita-Weats, Ry-vita, etc.).
Cakes, puddings, pastry, scones.
Ice cream, cream.
Dried fruits, tinned fruits, grapes.
Porridge, *cereals*—cornflakes, weet-bix, etc.
Spaghetti, macaroni, vermicelli.
Rice, sago, tapioca.
Baked beans, split peas, barley.
Fried foods—chips, etc.
Fatty meat, sausages, bacon, ham.
Olive oil, peanut oil, olives.
Dripping, lard.
Nuts, peanut butter.
Extra bread and butter.
Extra fruit.

Calories: 1,800. Protein: 85–90 g.

MANAGEMENT OF ECLAMPSIA

A Record of 125 Consecutive Cases

BY

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A SERIES of 125 consecutive cases of eclampsia admitted in the Chittaranjan Seva Sadan was treated with chlorpromazine hydrochloride and promezathin hydrochloride with no maternal mortality.

Since the last publication on this subject in this journal (Mitra and Dasgupta, 1957), certain modifications in the technic have been introduced, namely, the intravenous drip infusion in place of intermittent intramuscular injections of chlorpromazine and promezathin in the acute phase of the disease, and the addition of pethidine hydrochloride in selected cases.

MANAGEMENT

Routine Treatment. On admission, 12·5 mg. each of chlorpromazine (Largactil) and promezathin (Phenergan) is injected intravenously with 50 ml. of 5 per cent glucose solution to procure an immediate sedative effect.

Subsequently, within an hour, an intravenous 5 per cent glucose infusion of 540 ml. containing 50 mg. each of Largactil and Phenergan is started in drip form, the rate of which is controlled so as to maintain the sedative effect. This is continued and followed, if necessary, by a second pint of the same mixture till the blood pressure is stabilized at a lower level. In the majority of cases, the blood pressure is stabilized in 5 hours' time with one pint of the above fluid.

After the 5th hour, when the first pint of the injection is completed or after the 9th hour when the required second pint is finished, 25 mg. each of Largactil and Phenergan are given intramuscularly. It is repeated every 4 or 5 hours till the patient can take Largactil tablets (25 mg.) orally twice a day for 10–12 days. Phenergan is omitted in alternate injections.

The total amount of Largactil given parenterally in each case varied from 62·5 mg. to 237·5 mg., the average dose being 137·5 mg.

Adjuvant Therapy. With the glucose-chlorpromazine-promezathin drip, an intake of 540–1,080 ml. of water is insured. Oxygen is given by B.L.B. mask and the throat cleared of mucus by a sucker whenever necessary. The usual general measures including constant watching are carried out meticulously and are considered essential.

Additional sedatives were administered in 15 cases; in 2 of these cases where status eclampticus developed thiopentone sodium was injected intravenously. In the remaining 13 cases, pethedine hydrochloride 100 mg. to 200 mg. was given intramuscularly for recurrent fits (4 cases); secondary rise of blood pressure after the acute phase was controlled (3 cases) and post-partum secondary rise of blood pressure (6 cases).

Obstetric Treatment. Pelvic examination is carried out when the patient is fully sedated, provided she is in labour. No anaesthetic is used

for the purpose. When the cervix is dilating, a low rupture of membranes is done artificially.

Towards the end of the second stage, prophylactic ergometrine 0·25 mg. is injected intravenously during the delivery of the anterior shoulder. There was no case of post-partum haemorrhage or retained placenta.

Low forceps delivery and episiotomy is liberally employed under thiopentone sodium anaesthesia.

Lower segment Caesarean sections were done in 2 cases for cephalopelvic disproportion. There was no foetal or maternal death in these cases (Table I).

TABLE I

Mode of Delivery	No. of Cases	Percentage
Natural	45	45·4
Low forceps	47	47·4
Craniotomy	5	5·04
Caesarean section	2	2·02

Twenty-three cases were admitted post-partum. Three cases were discharged undelivered as all of them refused to stay in the hospital after the fits were controlled. They had natural delivery at their respective homes, one, six and eight weeks after discharge. There was no recurrence of fits. Three babies were born alive, of which one died after 3 days. The remaining two babies are living and healthy.

COMPLICATIONS

(1) *Tachycardia.* Intravenous injection of Largactil and Phenergan almost always produced a rise of pulse rate of more than 20 beats per minute in the first hour of treatment. In 19 cases, the rate increased to more than 160 per minute but came down to about 140 per minute in an hour's time. No special treatment was considered necessary. In 3 cases the initial pulse rate was about 160. Such high pulse rate was not regarded a contra-indication to this method of treatment.

Cardiac irregularity occurred in one case.

(2) *Hypotension.* In one case the blood pressure came down from 130/100 mm. of Hg to 70/50 mm. of Hg after the first intravenous injection but rallied subsequently. In other cases there was no alarming fall of blood pressure. An initial low blood pressure should be regarded as a contra-indication to the first I.V. dose. But none of these cases had a blood pressure below 130/90 mm. of Hg when admitted.

(3) *Oliguria and Anuria.* There was no case of anuria. A urinary output between 120 and 300 ml. in the first 24 hours was noted in 5 cases only. This shows a marked improvement as compared with the previous series (Mitra and Dasgupta, 1957).

TABLE II

Output (ml.)	Present Series (Per cent)	Previous Series (1957) (Per cent)
0–120	None	1 case
121–300	4	40
301–600	24	40
Above 600	72	20

This increase in output of urine was possibly due to intravenous glucose infusion.

(4) *Respiratory Complications.* No significant change in respiration was noted. In one case pulmonary oedema occurred and later she developed lobar pneumonia. One post-partum case developed severe respiratory depression following 3 fits in succession. There was no cyanosis, nor any evidence of pulmonary oedema.

(5) *Shock.* In one case, just following a low-forceps delivery, the systolic blood pressure suddenly came down from 170 mm. of Hg to 60 mm. of Hg. She recovered within an hour. There was no other case of shock either post-partum or after operation.

(6) *Psychosis.* Psychosis developed in 7 cases (5·6 per cent) from 2nd to 6th day of treatment and did not last for more than 5 days.

(7) *Hyperpyrexia* did not complicate any case.

(8) *Cardiovascular Accident*—Nil.

(9) *Post-partum Haemorrhage and Retainea Placenta*—Nil.

(10) *Jaundice*—Nil.

Results

Recovery. Consciousness was regained in 84·4 per cent cases within 24 hours; in 14·4 per cent cases within 24 to 36 hours, and in one case the unconsciousness persisted for more than 36 hours.

Control of Fits. There was no fit after the treatment was started in 45 cases (36 per cent). More than 15 fits occurred in 4 cases—two of which developed status eclampticus and were treated with intravenous thiopentone sodium.

Table III

Control of Fits

	No. of Cases	Percentage
No fit	45	36
Controlled in 6 hours ..	13	10·4
Controlled in 7–13 hours ..	58	46·4
Controlled in 14–24 hours ..	7	5·6
Controlled in 25–36 hours ..	2	1·6

Fits were controlled in 13 hours in 116 cases (93 per cent) (Table III). Perhaps the fits could have been controlled earlier by increasing the doses of Largactil and Phenergan and by the routine use of pethidine in every case.

As the results obtained in the present series were so encouraging, no further change in the treatment was contemplated.

Maternal Mortality. There was no death in this series.

Foetal Loss. The uncorrected foetal wastage in this series, excluding the post-partum case and undelivered cases, was 53·5 per cent (53 cases). Of these, the foetal heart sounds were inaudible in 12 cases before the treatment was started and, of the remaining 41 cases, 25 babies were premature, weighing between 3 pounds 4 ounces and 5 pounds. The corrected foetal wastage is 16 per cent (Table IV).

Table IV

Corrected Foetal Wastage

	Per cent	
Stillbirth	8	(8 cases)
Neonatal mortality	8	(8 cases)
Total mortality	16	(16 cases)

Summary

(1) One hundred and twenty-five consecutive cases of eclampsia were treated with chlorpromazine and promezathin.

(2) There was no maternal death.

(3) Corrected foetal wastage was 16 per cent.

(4) Serious complications had been greatly minimized by the modified technique.

(5) In 93 per cent of cases, fits were controlled within 13 hours from the onset of treatment.

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BILHARZIASIS OF THE PREGNANT UTERUS

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SCHISTOSOMIASIS (bilharziasis) is a parasitic infestation which may affect a host of body organs but whose brunt usually falls on the urinary or the intestinal tracts. Even in localities where the disease is endemic such as Egypt, South and East Africa, South America and Japan, involvement of the female genital organs is comparatively rare. Few papers dealing with gynaecological bilharziasis have appeared in the literature, and in some of them the effect of the disease on the female reproductive function was briefly discussed. Charlewood, Shippel and Renton (1949) described a case of post-partum uterine fibrosis in a woman who suffered from vesical bilharziasis and thought that the fibrosis of the uterus might have been of bilharzial origin but they could find no bilharzia ova in the uterus or in any other part of the genital tract. Narabayashi (1914) reported a unique case in which the worm of *Schistosoma japonicum* passed through the placenta and infested the foetus. Bilharzial infestation of the pregnant uterus, however, has never before been demonstrated.

We have lately been removing small pieces of tissue from the cervix and the upper and lower segments of the pregnant uterus in order to investigate the arrangement of the muscle and connective tissue fibres. In two of the cases studied bilharzia ova were accidentally encountered in the wall of the pregnant uterus.

CASE REPORTS

Case 1

Patient R.A.H. (Hosp. No. M 12624/57), aged 20 years, was admitted on 21st June, 1957, with the diagnosis of inevitable miscarriage. She had been married for 2 years and had had 1 full-term normal delivery. She had started to menstruate at the age of 12; her periods had always been regular and normal in amount and duration but accompanied with dull, aching, suprapubic pain. She had suffered from haematuria and other bladder symptoms at the early age of 7, had been found to have urinary bilharziasis and given a course of tartar emetic injections following which all her urinary complaints were permanently relieved. On admission she was 24-weeks pregnant and complained of moderate vaginal bleeding, of hypogastric and low back pains and of watery vaginal discharge. On examination her pulse was 88, temperature 37·6, blood pressure 120/80 and her urine was albumin and sugar free. Examination of the heart, chest and abdomen revealed normal findings. On vaginal examination the cervix was found 2-fingers dilated, the membranes ruptured and a leg was protruding through the external os. A quinine-pituitrin course was soon followed by the expulsion of a small macerated foetus. Since the placenta was retained and bleeding continued it was decided to evacuate the uterus under general anaesthesia. After evacuation two small pieces of tissue were removed, one from the region of the external and one from the region of the internal cervical os. This is at present routinely done after evacuation as a part of a detailed investigation of the normal structure of the pregnant uterus. In this case the microscopical examination of the tissue removed from the region of the external os revealed the presence of massive bilharzial infestation (Figs. 1 and 2).

Histological Report. The specimen is partly covered by stratified squamous epithelium and partly by high columnar epithelium with racemose glands. Directly underneath the epithelium, especially the stratified, there is a large number of bilharzia ova (about 50 in one section). They are arranged mostly in big groups, some are scattered and few are embedded deeply in the substance of the cervix.

There is oedema and congestion of the stroma, an appearance consistent with the histological picture of pregnancy. Van Gieson stain shows that the bulk of the cervical tissue is fibrous, the muscle tissue being very scanty. The ova are mostly degenerate and calcified, denoting old infection. There is cellular reaction mostly fibroblastic in relation to the ova; this reaction is minimal where the ova are condensed in masses. There is also superficial ulceration of the epithelium in relation to some ova which may thus easily pass to the outside with the discharge. There is mild superficial chronic septic infection with some polymorphs and many plasma cells. Eosinophils are very scarce.

Following this unexpected finding further investigations were carried out. Meticulous examination of the urine and stools failed to disclose the presence of bilharzia ova. Cystoscopy revealed the presence of "very mild chronic cystitis with no typical bilharzial lesions in the left part of the posterior superior bladder wall and in the bladder base". Intravenous pyelography and kidney function tests revealed normal findings.

Case 2

Patient R.A.M. (Hosp. No. M 14100/57), aged 25 years, was admitted on 11th July, 1957, early in the first stage of labour. She had been married for 7 years and had 2 living children both delivered by lower segment Caesarean section for general pelvic contraction. The last section had been performed two and half years previously. She had had one abortion of 3 months shortly after marriage. She had started to menstruate at the age of 13 years and her periods had always been regular but she used to have menorrhagia and congestive dysmennorrhoea. She had suffered from haematuria and dysuria at the age of 9 years, was found to have vesical bilharziasis and was treated by tartar emetic injections which completely cured her urinary symptoms. Her present pregnancy was uneventful.

On examination she was found to have a normal full-term pregnancy, the presentation was cephalic, the position was left occipito-anterior and the head was high above the brim. Uterine contractions had started a few hours before admission. Her pulse was 110, temperature 37° C. and blood pressure 110/70. The foetal heart sounds were of normal rate and rhythm. The urine was sugar and albumin free. On vaginal examination the cervix was 2-fingers dilated and the membranes were intact. There was evidence of pelvic contraction at all pelvic straits. The Müller-Kerr manœuvre revealed the presence of second degree cephalopelvic disproportion.

A lower segment Caesarean section was performed by the first author and a male living child weighing 3·2 Kg. was delivered. Sterilization was performed at the patient's own request. The incision in the lower segment was made longitudinally in the middle line extending upwards for 1 cm. above the junction of the lower and upper segments and downwards for 1 cm. below the junction of the lower segment and the cervix. A slice of the uterine wall was removed along the whole length of the incision and was as usual sent for histological examination. This showed that the lower uterine segment was heavily infested with bilharzia ova (Figs. 3 and 4). When the histological report was received the placenta was not available for examination. The foetus, however, was healthy and showed no evidence of bilharziasis or other disease.

Histological Report. The lower uterine segment contains several (10 in one section) bilharzia ova. Five of them are very superficial, being covered only by the epithelium. They are calcified and appear dark blue in haematoxylin and eosin sections. The rest are embedded in the submucous layer (Fig. 3), are mostly degenerate and some are calcified. No cellular reaction is present in relation to the ova. There is septic infection and oedema of the mucosa and muscle tissue. There is also decidual reaction in the superficial layers of the mucosal lining of the lower uterine segment (Fig. 4).

In spite of careful examination no bilharzia ova could be detected in the patient's urine or stools. The patient refused cystoscopy saying that she had no urinary symptoms whatever. Intravenous pyelography and kidney function tests showed normal findings.

Comment

Bilharziasis of the corpus uteri is an exceedingly rare condition. Te Groen (1939) found in his vast material only 2 cases of bilharzial endometritis. Mahfouz (1949) described one case in which bilharzia ova were detected in the substance of a uterine fibromyoma. Charlewood *et al.* (1949), in their study of gynaecological schistosomiasis in South Africa, which covered the period from 1911 to 1948, mentioned that bilharzia ova were found in the body of the uterus in only 4 cases. In one of them the ova were found in small nodular structures on the surface of the uterus. In the 3 other cases they were found in the endometrium which in one case was metropathic, in another it had undergone metaplasia to a squamous type and in the

FIG. 1

Note the 3 degenerate bilharzia ova in the subepithelial connective tissue of the portio vaginalis of the cervix.

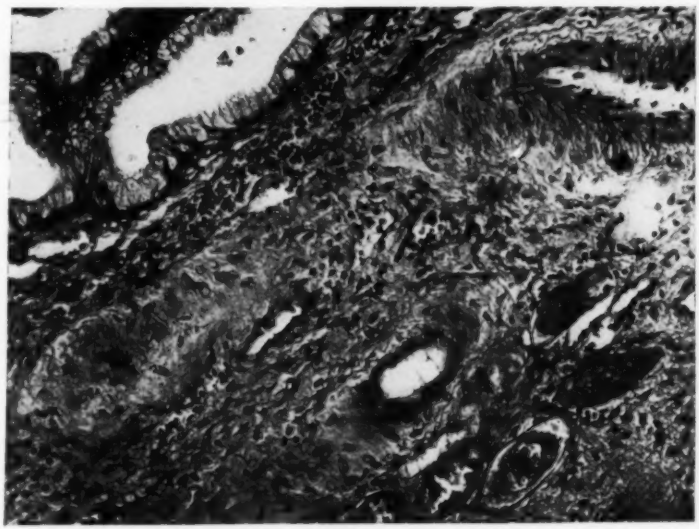

FIG. 2

Note the 5 bilharzia ova longitudinally cut and arranged in a line. One of them shows a terminal spine denoting haematobium infection.

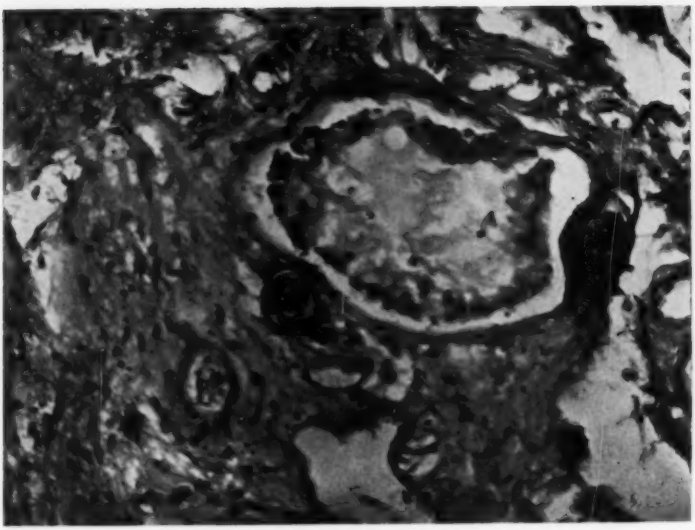

FIG. 3

Section in the lower uterine segment showing 2 bilharzia ova in the wall of a gland and apparent oedema in the connective tissue stroma.

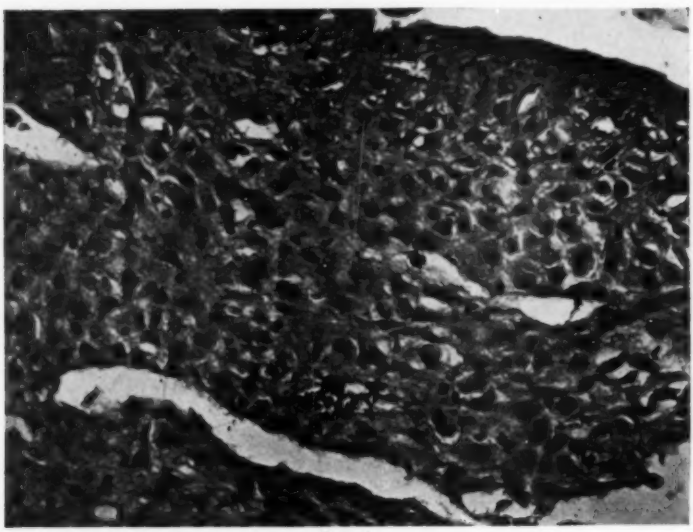

FIG. 4

Note the superficial decidual reaction in the mucosa of the lower uterine segment.

third a squamous cell carcinoma of the uterus had developed. Magdi and Hefnawi (1951) found among 17,344 gynaecological patients in Egypt only one case of bilharziasis of the endometrium in spite of the large number of curettages performed. They stated their belief that "it is inconceivable that the parasite which instinctively seeks an excretory organ of suitable nature to lay its eggs for propagation of the species should seek the uterus which being a thick-walled muscular organ is entirely unsuited for the purpose". Madden (1922) stated that he had never seen involvement of the uterine mucous membrane in bilharzial patients.

Bilharziasis of the cervix is less uncommon. Charlewood *et al.* (1949) described 16 cases while Magdi and Hefnawi (1951) encountered 18. The recent employment of routine colposcopy in our clinic has led to the discovery of a number of cases which were undetectable by inspection and palpation (Youssef, 1957). Sterility is often present in bilharzial patients (Girges, 1934; Charlewood *et al.*, 1949), especially in cases of cervical bilharziasis where the diseased cervix seems to present a barrier to successful insemination.

Because of the rarity of uterine bilharziasis and the prevalence of sterility in bilharzial patients it is not difficult to understand why bilharziasis of the pregnant uterus has not heretofore been reported. On the other hand it is surprising that in a comparatively small series of pregnant uteri subjected to biopsy bilharzia ova could be demonstrated in 2 cases. This could be a matter of mere coincidence but it must lead to the suspicion that the previous failure to detect bilharziasis of the pregnant uterus in infested localities might have been due to the fact that in practice the indications for microscopic examination of the pregnant uterus are indeed very few.

An interesting feature of our two cases is the finding that the urinary bilharziasis which had been present in both disappeared completely following previous tartar emetic treatment while the bilharzial lesions in the uterus remained. The reason for this may be that ova when embedded in the thick muscular wall of the uterus are not so accessible to the action of the drug. A further point of interest in the first case is the fact that she presented herself with inevitable miscarriage of a dead foetus. It is widely believed that bilharzial patients in general are more liable to miscarriage, premature labour and intra-uterine foetal death, this being due to systemic intoxication, anaemia or kidney failure rather than to any local effect on the genital tract (Girges, 1934; Charlewood *et al.*, 1949). In our case none of these factors was present and since the foetus and placenta could not be examined it is not possible to tell whether the foetal death and miscarriage were in any way related to the bilharzial condition.

Summary

Two cases of bilharziasis of the pregnant uterus, the first to be reported in the world literature, are described in detail. The causes of the extreme rarity of this pathological entity are discussed.

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PREGNANCY FOLLOWING FUNDECTOMY FOR ADENOMYOSIS

Report of a Case

BY

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SOME twenty-five years ago, there was an impression among gynaecologists working in India that endometriosis in any form was rare in Indian women. But there is no doubt now, that this condition is commonly met with, and at any age of the child-bearing period. The significance of endometriosis occurring in early reproductive life is important whether it is considered to be the cause or effect of infertility. Several workers such as Scott (1944), Ware (1950) and Whitehouse and Bates (1955) have reported pregnancy following the excision of the affected area. The last two papers refer only to cases of external endometriosis followed by pregnancy. Scott reported 12 cases of adenomyosis associated with pregnancy. The average age in his group was 36·1 years. Lock (1946) reports two cases of adenomyosis, where the women conceived and became the mothers of near-term infants. In one of the above cases, fundectomy had been done with removal of two-thirds of the uterus.

A case of adenomyosis, developing symptoms at the early age of 21 is presented here. Pregnancy followed fundectomy undertaken for dysmenorrhoea.

Wahida Begum, aged 24, married five years, a nullipara, was admitted on 1st June, 1956, with a history of severe dysmenorrhoea for the past 3 years. Her first menses occurred at the age of 12 and the subsequent cycles were normal. She sought relief for menorrhagia, dyspareunia and dysmenorrhoea which were gradually getting worse. Examination revealed a uniformly enlarged hard and tender uterus. Diagnosis of adenomyosis was made. At laparotomy, the uterus was found enlarged to 14 weeks size with fine capillary injection and thickening of the isthmial ends of the tubes. No discrete myoma could be palpated. Both the ovaries were enlarged to about four times the normal size. Because of her age and infertility, conservative surgery was indicated. Fundectomy was performed extending to within 1·5 cm. of the uterine ends of the tubes. The wedge excised was 5 cm. wide and 6 cm. long. The apex reached the internal os exposing the endometrium which was hyperplastic. The posterior wall of the uterus at the level of the internal os was 6 cm. thick and anteriorly 4 cm. in thickness. The cut surface of the uterine wall was studded with the tell-tale depressed areas containing brownish stale blood. The ovaries were split along the free border for inspection. The left one contained several corpora lutea in various stages of regression. The residual uterus was suspended by Olshausen's method.

The patient made an uneventful recovery. An attempt was made to suppress ovulation with oestrogens, but the patient could not tolerate

more than 20 mg. of stilboestrol and she had to discontinue this form of treatment.

The patient was lost sight of till she reported with a 24-weeks pregnancy on 1st August, 1957. On enquiry she stated that she had enjoyed complete relief from dysmenorrhoea after the operation. After about 8 menstrual periods, which were normal, she had conceived.

On vaginal examination, the cervix was found to be partly effaced. The patient complained of discomfort in the lower abdomen ever since she had missed the first four menstrual periods. She was admitted at 34 weeks into the hospital for rest and observation. The uterus was tense and the cervix was completely effaced. At the end of 36 weeks, she spontaneously ruptured her membranes. Since no uterine contractions occurred for six hours, she was delivered by Caesarean section of a live female infant weighing 5 pounds 1 ounce (2,325 g.). There was no naked eye evidence of adenomyosis in the pelvis. Filamentous adhesions were present between the omentum and the anterior surface of the uterus. There was a finger-like depression in the centre of the fundus and the tubes were seen to be inserted one finger's breadth away on either side of the middle line. Both the anterior and posterior surfaces of the uterus showed wavy longitudinal scars extending right up to the internal os. Three depressions were noted along the side of the scar in front, at the site where the mattress sutures had been tied.

The mother and the baby were discharged well on the 18th day after the operation.

Summary

(1) A case of adenomyosis with severe dysmenorrhoea in a girl of 24 is reported.

(2) Since the adenomyosis had caused uniform enlargement of the uterus, fundectomy was undertaken in order to conserve the function.

(3) Pregnancy had promptly followed the operation. A near-term infant was delivered by Caesarean section.

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OXYURIS GRANULOMATA OF THE FALLOPIAN TUBE AND PERITONEAL SURFACE OF AN OVARIAN CYST

BY

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GRANULOMATOUS lesions due to *Oxyuris vermicularis* are very rare in any site. Symmers (1950), in a review of the pathology of oxyuriasis, found only 16 reported cases of pelvic peritoneal lesions and added 2 further instances. All the pelvic peritoneal lesions have occurred in females and have usually been found incidentally in patients with other pelvic pathology, the granulomata rarely giving rise to symptoms. In the case reported here the condition was found during investigation for symptoms which could not be regarded as due to the infestation.

CLINICAL FINDINGS

A married woman of 33 years attended the Gynaecological Out-Patient Department complaining of menorrhagia and metrorrhagia for one year. Her menstrual cycle was 4/30, but during the year before her attendance it had become 14/14–21. There was very slight intermenstrual leucorrhoea, but no other complaints. She had had one normal confinement 3 years previously.

On examination, there were no signs of any general disease. The vulva and vagina were normal, the cervix was infected and eroded, and the uterus retroverted and retro-flexed.

The appendages were not satisfactorily palpated owing to the patient's tenseness. Cervical smears showed no evidence of malignant cells. A provisional diagnosis of functional uterine bleeding with chronic cervicitis was made and she was put on the waiting list for examination under anaesthesia and curettage.

Under anaesthesia, a cyst was found in the right appendage which was not considered large enough to justify removal. The uterus was curetted and the cervix cauterized. The curettings histologically consisted of normal secretory endometrium.

Two months later she was symptom-free and the menstrual cycle had reverted to a normal rhythm of 4/30. The cyst had apparently, however, increased in size, was less mobile and had become tender. She was, therefore, re-admitted to hospital for laparotomy.

At operation a cyst approximately 2×3 inches replaced the left ovary. The distal half of the Fallopian tube was thickened. On close inspection pin-head sized nodules were seen on the surface of the cyst and a few larger nodules in the distal end of the tube. The other pelvic organs were normal. Left salpingo-oöphorectomy was carried out and the appendix was also removed as it showed signs of chronic inflammation.

The specimen consisted of a roughly round, bilocular cyst, measuring 5 cm. across, and the outer portion of the Fallopian tube 4·5 cm. long, the fimbriae of which appeared normal.

Scattered over the outer surface of the cyst were approximately 12 small white nodules

FIG. 1

Section of cyst wall showing the lining of the cyst and a granulomatous nodule on the peritoneal surface. ×26.

FIG. 2

Granuloma with peripheral fibrosis and central giant cells. ×100.

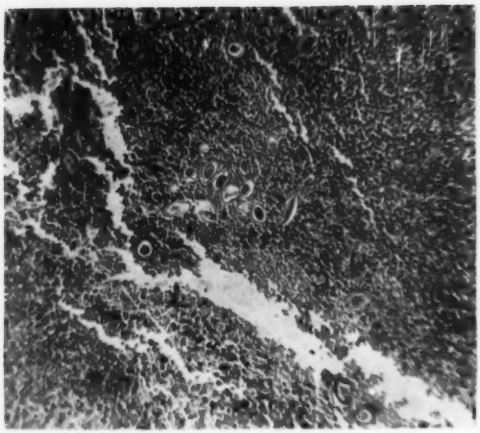

FIG. 3
Ova in necrotic centre of granuloma on Fallopian tube. ×90.

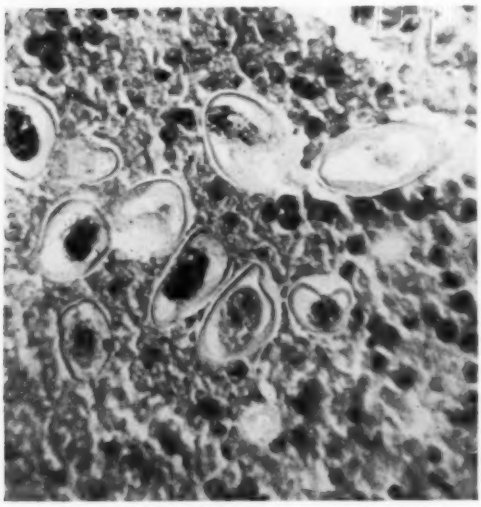

FIG. 4
Group of ova. ×380.

averaging 2–3 mm. across. The cyst wall was 2–4 mm. thick and smooth on its inner surface and bilocular. On the peritoneal surface of the fimbrial end of the tube were two projecting nodules 1 and 0·5 cm. across, the centres of which consisted of slightly yellowish necrotic material.

Histological examination showed that the cyst was a typical simple pseudo-mucinous cyst-adenoma. Over the peritoneal surface of the cyst were many small granulomatous lesions (Fig. 1), these being far more numerous than had been suspected. As many as eight granulomata ½–2 mm. in diameter were present in a single section. These had a thin peripheral zone of fibrous tissue infiltrated with a small number of lymphocytes and, inside this, scattered lymphocytes, reticulo-endothelial cells and sometimes multi-nucleated giant cells surrounding a central necrotic area of eosinophilic tissue. A few of these small granulomata consisted largely of reticulo-endothelial cells and giant cells with no visible necrotic centre (Fig. 2). The larger nodules on the tube were sub-peritoneal, consisting of a thin outer layer of fibrous tissue sparsely infiltrated with lymphocytes, reticulo-endothelial cells and a very few plasma cells and eosinophils, and a central necrotic eosinophilic mass in which many well preserved, as well as degenerate eggs of oxyuris were present (Figs. 3 and 4). The necrotic centre consisted of eosinophilic debris in which outlines of numerous degenerate cells were visible.

The eggs had the following characteristics. They were roughly oval, being 55–60 μ long and 30 μ wide. They had a well-defined capsule and many showed one convex and one flattened, almost straight, side. In the well-preserved specimens the granular, darkly staining embryo of oval or coiled shape was easily identified. The irregularities of shape so typical of some oxyuris eggs were present.

Numerous sections of the cyst wall showed a focus of necrosis at some level in all the small granulomata and eggs in very small numbers in some of them. No evidence of an adult worm was found in any section.

The entire appendix was examined histologically without an adult worm or eggs being seen.

Post-operative Progress. Recovery from the operation was interrupted by an episode of chest infection and later by urinary infection, but at follow-up the wound was well healed and she was free of symptoms. During convalescence a search was made for thread worms and ova in faeces, anal, vaginal and cervical swabs and all the investigations were negative.

Discussion

This case is similar to those previously reported in that the infestation with oxyuris was an accidental finding, though this is the first instance, to our knowledge, of granulomatous lesions over the surface of an ovarian cyst.

The histological findings are also similar to those previously described. In roughly half the reported cases numerous eosinophil leucocytes are present in the granulomata. When these are absent and only small lesions are seen, showing, in a casual section, no central necrosis, it is clear they could readily be mistaken for tuberculous granulomata, but, if several lesions are seen, little likelihood of this error should arise.

It is presumed that in this case, as in other pelvic peritoneal lesions, the adult worm has gained access to the peritoneum via the genital tract. Since Symmer's review, Nairn and Duguid (1954) and Schenken and Tamisiea (1956) have reported granulomatous endometritis due to oxyuris, so that these lesions have now been reported in all parts of the female genital tract, from the cervix to the peritoneum.

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PREGNANCY COMPLICATED BY A RETRO-PERITONEAL TUMOUR OF POSSIBLE MESONEPHRIC ORIGIN

BY

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IT is generally accepted that certain cystic tumours of the mesosalpinx, broad ligament and antero-lateral vaginal wall have their origin in remnants of the mesonephric (Wolffian) duct. That these vestigial remnants may give rise to solid tumours is perhaps less well known. Such a tumour, complicating pregnancy and producing a potential obstruction to labour, is to be described.

CASE HISTORY

The patient concerned was aged 28 and expecting to have her fifth baby at home on the 10th August, 1957. Her four previous confinements had been normal, and her health before and during the present pregnancy had been good.

She was admitted to St. Stephen's Hospital on the 6th September, 1957, because she had failed to go into labour following spontaneous rupture of the membranes ten days previously. When examined on admission no abnormality was discovered apart from a slightly raised blood pressure, although it was noted that "the rectum was full of hard faeces". A medical induction of labour was administered without success. A second vaginal examination was then made which revealed the following points:

(1) There was a small cyst half an inch in diameter in the left lateral vaginal wall about one and a half inches from the introitus.

(2) There was a fixed bony-hard mass about the size of a cricket ball, situated in the recto-vaginal septum below the presenting part.

(3) The cervix was undilated and normal.

These findings were confirmed by examination under anaesthesia which also showed that there was no abnormality in the vaginal or rectal mucous membrane.

As an insuperable obstruction to vaginal delivery was present a lower segment Caesarean section was performed and a live female child weighing 8¼ pounds was delivered. Following the Caesarean section the uterus was eventrated and the pouch of Douglas explored. This revealed that the tumour was attached to the upper third of the posterior vaginal wall slightly to the right of the midline. It was covered with peritoneum and partly obliterated the pouch of Douglas. There were numerous firm nodules on the peritoneum of the pouch of Douglas and in the right utero-sacral ligament with seedling deposits on the surface of the rectum and lower sigmoid colon up to the level of the sacral promontory. The uterus, tubes, and both ovaries were normal except that there was a seedling deposit on the surface of the right ovary. There was no free fluid and no evidence of spread outside the true pelvis in the general peritoneal cavity, para-aortic glands or liver. A biopsy was taken from the nodule in the right utero-sacral ligament and the abdomen was closed.

The pathological report on the biopsy was that the tumour resembled a papilliferous cystadenoma with numerous areas of degeneration and calcification. The opinion was expressed that the tumour was benign. A second pathological opinion was in agreement with this.

Further investigations were carried out including sigmoidoscopy, intravenous pyelography, and cystoscopy. They did not add to our knowledge of the origins of the tumour, but did confirm that the lower bowel although firmly adherent to the tumour had an intact mucous membrane. The calcified nature of the tumour was demonstrated by the intravenous pyelogram. The patient was examined under anaesthesia again and it seemed that the tumour had increased slightly in size during the previous 4 weeks. There was a small granular area in the posterior vaginal fornix which was suggestive of commencing ulceration.

It was decided that a radical surgical procedure should be undertaken to remove the tumour, as it was considered that the previous operative findings of obvious secondary deposits outweighed the benign histological appearance in one of those deposits. Accordingly a posterior exenteration was performed on the 16th October, 1957. The findings were substantially the same as before. The uterus, tubes, ovaries, posterior vaginal wall, lower sigmoid colon and rectum were removed by a combined abdominal and perineal approach. A left iliac colostomy was performed. Some difficulty was encountered in freeing the bladder from the fresh lower segment scar, but otherwise the operation was straightforward.

FIG. 1
The operation specimen. Bisected longitudinally.

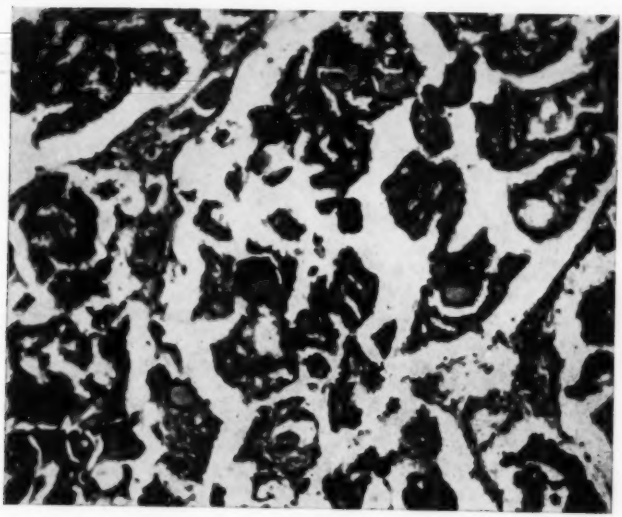

FIG. 2
Microscopic section of the tumour, ×24.

The patient made a very satisfactory physical and mental recovery from this operation, apart from the usual difficulty in emptying her bladder. She left hospital on the 25th November, six weeks after the second operation. She was seen in Out-patients four weeks later when she looked and felt very well. Her recovery was such that she had been able to go out dancing with her husband.

Pathology

The pathology of the specimen was as follows:

(1) The tumour was of a lobulated, partly cystic type measuring $12 \times 6 \times 6$ centimetres. Histologically the main tumour resembled that of the original biopsy being of a papilliferous cystadenomatous type with numerous foci of degeneration and calcification. The muscular wall of the rectum was invaded by growth, but not the mucous membrane (Figs. 1 and 2).

(2) Section of the ovaries showed no growth. Later serial section of the right ovary revealed a surface seedling only.

(3) The vaginal cyst, which was separate from the large tumour, was a simple cyst lined by cubical epithelium.

(4) There were no vestigial remnants to be seen in the region of the cervix or vaginal vault.

(5) Having examined the whole specimen the pathologist expressed the opinion that the tumour must be considered to be malignant.

Comment

There were two main problems in connexion with this case. Firstly, the clinical problem of how to deal with such a tumour in a girl of 28. The pathologist had reported on the biopsy that the tumour was a benign one, but obvious secondary deposits, confined to the true pelvis, had been observed during the Caesarean section. In coming to a decision we allowed the operative findings to outweigh the pathological report. Local removal of the tumour was out of the question, and the use of radiotherapy was not entertained.

Secondly, there was the pathological problem of the origin of the tumour. By far the most likely explanation of such a tumour would be that it was a secondary deposit from a papilliferous tumour of the ovary. No such primary tumour could be discovered on careful macroscopic and microscopic examination of the ovaries, the only lesion present being the surface seedling described on the right ovary.

The possibility was then considered that the tumour might have arisen from vestigial remnants in the vaginal vault. The existence of mesonephric elements in the mesosalpinx, broad ligaments and antero-lateral vaginal walls is well known. Mesonephric elements have also been described in the cervix and vaginal vault by Meyer (1900) and more recently by Wolfe (1940) and Huffman (1948). The latter author found such vestiges in 5 out of 1,192 cervices examined. They apparently take the form of small tubular structures with bilateral ramifications and invaginations almost encircling the cervix and extending into the lateral fornices of the vagina.

It is in the cervix and vaginal vault that the vestigial mesonephric elements apparently show the most frequent tendency to proliferative and neoplastic activity and certain rare pathological lesions may result in these locations. Cysts, cystadenomata composed of clusters of tubules, intracystic papillary growths, and adenocarcinomata, have been described. Sometimes a direct connexion between the tumour and a mesonephric element has been demonstrated.

Novak, Woodruff and Novak (1954) described 3 papillary lesions of the vaginal vault which they believed were of mesonephric origin. Two of these tumours were malignant.

The tumour that I have described resembles those mentioned by Novak *et al.* in certain clinical features and in histological appearance. Although no direct continuity could be demonstrated with a mesonephric element in this case, there was a small vaginal cyst present which could have been of mesonephric origin.

Summary

(1) The case history and pathology of a retro-peritoneal tumour complicating pregnancy are described.

(2) Reasons are advanced for believing that the tumour arose in vestigial mesonephric elements in the vaginal vault.

Acknowledgments

I should like to acknowledge the great help that I received from my colleagues Mr. Howard Jayne, M.S., F.R.C.S., and Dr. Marjorie Gillespie with the clinical and pathological aspects of this case.

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MIXED MESENCHYMAL TUMOURS OF THE BODY OF THE UTERUS

A Report of Two Cases

BY

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MIXED mesenchymal tumours have been reported as comparative rarities for about a hundred years (Meikle, 1936) and under an even greater number of names (McFarland, 1935). Published new cases are still infrequent and after a century of speculation their aetiology remains obscure; indeed, precise definition of these peculiar neoplasms is not yet universally agreed.

Possibly the most important clinical observation in their study is the recognition of a relationship between the site of the tumour and the age of the patient. Wilfred Shaw gave a clear account of this correlation 30 years ago in this *Journal*. As a rule the growth arises in the vaginal wall in infants, in the uterine cervix in women in the reproductive period, and in the body of the uterus in those past the climacteric. Shaw believed that in adults the tumour was relatively more frequent in the cervix, in parallel with carcinoma, but more recent papers, e.g., in Wurtz (1949), and Symmonds and Dockerty (1955) suggest that the corporeal neoplasm is the commoner.

The two examples presented here were both in patients who had passed the menopause. In the first case, the evidence pointed strongly to a uterine origin although the exact site was not finally established, in the second the tumour arose from the fundus of the uterine body.

CASE REPORTS

Case 1

Mrs. E.T., aged 51 years, para-4, was admitted to the gynaecological wards of Glasgow Royal Infirmary on 17th September, 1953, with a complaint of infrequent and irregular vaginal bleeding over the last 3 years. The last haemorrhage had been 3 months before admission, and during that time there had been a foul and occasionally blood-stained vaginal discharge. The menopause had been early at 37 years in 1938.

On admission the patient was very obese, pale and ill. Her blood pressure was 160/80 mm. Hg, pulse rate 116/min. and haemoglobin level 7 g. per cent. General examination was otherwise negative. Under anaesthesia pelvic examination disclosed the vaginal vault completely filled with friable and necrotic malignant-looking tissue, and nothing was done beyond sending a small piece for histological examination. Her obesity prevented satisfactory palpation of the pelvic organs.

Treatment was initiated by blood transfusion, and a course of antibiotics; followed by a course of deep X-ray therapy in twenty treatments in an attempt to reduce the size of the florid vaginal growth. There was some improvement and the patient was sent home for three weeks and then re-admitted for radium therapy. At the time of insertion of radium on 22nd December, 1953, the vaginal vault and the upper half of the anterior wall of the vagina were found to be replaced by growth, but the posterior wall was clear. Owing to loss of weight in the patient, a tumour presumed to be uterine could now be made out. It was palpable 3-fingers above the symphysis pubis and occupied most of the pelvis. The cervical canal and even the cervix itself could not be identified; as a palliative measure 20 mg. of radium were inserted in each vaginal fornix for 160 hours. This produced considerable improvement, the discharge became much less and the patient was in a condition to be sent home on

3rd January, 1954. On 24th January, 1954, she was seen again when she complained of constant pain controlled only by morphine given by her doctor. The abdomen at this stage was tense, tender and enlarged in the lower half.

On the next day the patient died suddenly and unexpectedly at home.

Comment. It is unfortunate that necropsy was not obtained. Treatment in this case was palliative from the start and surgery was never considered because of the patient's obesity and the advancement of the disease. It is not possible to say with certainty that this tumour arose from the uterus itself, but the clinical features render it likely.

Pathology of Biopsy Material: The specimen comprised four irregular blood-shot fragments of granular white tissue, the largest measuring 20×10×5 mm. Microscopically each consisted of anaplastic predominantly round-cell malignant tumour. Normal uterine and cervical structures were absent. In most fields the tumour nuclei were vesicular and closely set, cytoplasmic definition being deficient. Locally, oedema produced a spindle-cell appearance. In some areas there were small circumscribed deposits of fibrin. These were surrounded by cells with trachychromatic nuclei and resembling adenocarcinoma. This appearance however was false because basement membranes were absent from the formations (Fig. 1). Dispersed throughout the growth were loose aggregates of large round cells with deeply staining oxyphile cytoplasm (Fig. 2). These and some of the spindle-cells exhibited cross-striations when suitably stained (Fig. 3). Mitoses were very numerous throughout the growth and degenerative changes were extensive.

Case 2

Mrs. M.C., aged 63 years, nulliparous, was admitted to the surgical wards of Law Hospital on 13th February, 1957, with a complaint of abdominal swelling of 2-months duration and a dragging sensation in the left hypochondrium. The abdomen was found to be moderately distended by ascites and a mass thought to be the liver was palpable in the subcostal region. Her general condition was fair: her blood pressure was 200/120 mm. Hg, and haemoglobin 10·9 g. per cent. Examination was otherwise inconclusive and after a week's observation a tentative diagnosis of cirrhosis of the liver was adopted. The patient, already a little dyspnoeic, was transferred to a medical ward. Respiratory distress soon became urgent because of the rapidly increasing ascites and in the ensuing few weeks repeated paracentesis was necessary, about 6,000 ml. of straw-colour fluid being removed on three occasions. After drainage, a large smooth mass was palpable in the upper left quadrant of the abdomen and malignant renal tumour was suspected. The patient's general condition was by now deteriorating quickly, and she died in the ward on 19th April, 1957.

Comment. Gynaecological opinion was not sought in this case because there was, unusually, no vaginal bleeding, and treatment for tumour was not given at any time. Even if the correct diagnosis had been reached, it is unlikely that anything other than palliative irradiation could have been exhibited.

Necropsy. The abdomen was rigid and protuberant in sharp contrast to the general cachexia. The whole of the peritoneal membrane was encrusted by firm creamy pink nodular tumour, and the remaining cavity was filled with glairy fluid. The largest discrete tumour nodules measured 3 cm. diameter, but in most regions the deposits were smaller and fused into masses. The uterus was symmetrically enlarged by what appeared to be a submucous fibroid tumour. This growth arose from the fundus and measured 10×9×6 cm. Dissection however revealed a granular white and patchily haemorrhagic structure, quite unlike the familiar leiomyoma. Encapsulation was absent and extension of the neoplasm could be traced through the uterine wall into the pelvic peritoneal deposits. The atrophic ovaries bore small epiphytic tumour nodules which did not resemble primary tumour in any way. The remaining abdominal viscera were found to be clear of tumour after meticulous search. Lymph nodes in this region were difficult to identify with certainty; those found were atrophic.

In the thorax, penetration of the left leaf of the diaphragm by malignant tumour was evident, and several small pale greyish-pink metastases were discovered in the upper lobes of both lungs. The air passages were free from tumour to the limits of dissection, and the mediastinal lymph nodes were also devoid of visible metastases.

The structures of the head and neck were natural with the exception of the thyroid gland, which contained several encapsulated brown nodules. The bones of the skull, thorax and

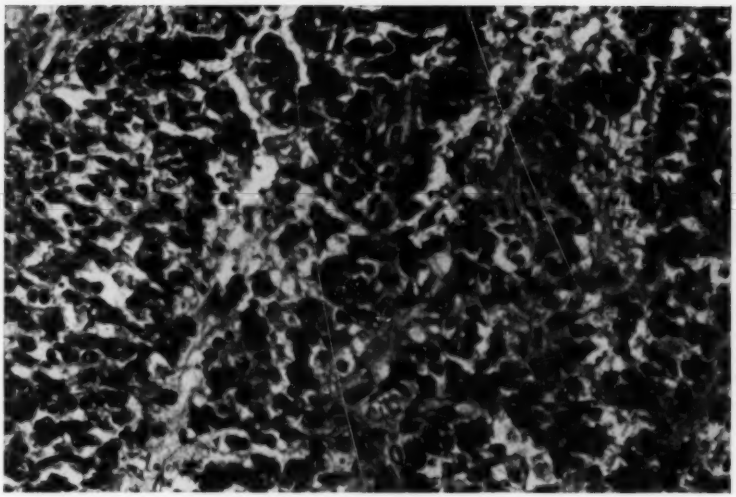

FIG. 1

Case 1. Pseudo-glandular arrangement of the tumour-cells. Note the absence of basement membranes. H. & E. ×380.

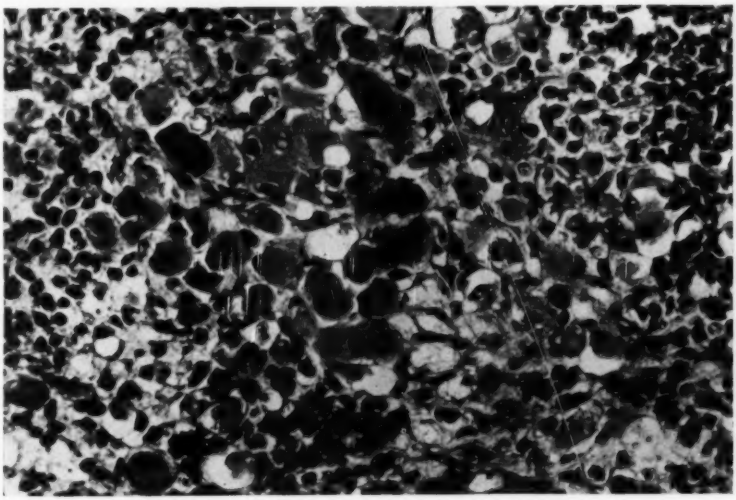

FIG. 2

Case 1. A group of large myoid cells occupies the centre of the field. H. & E. ×380.

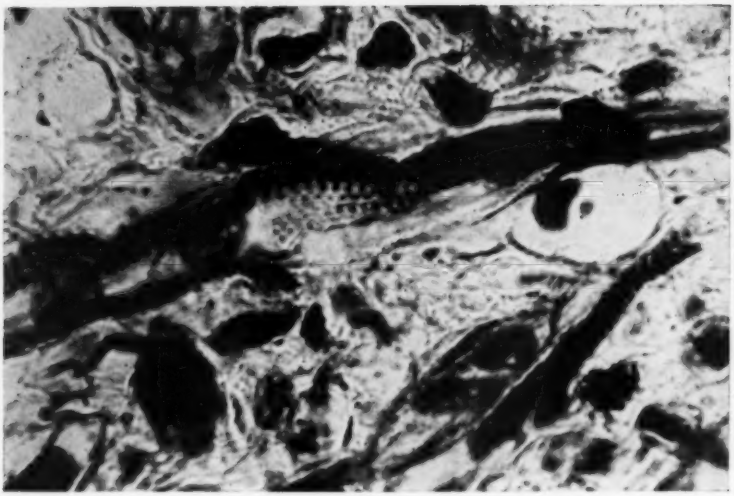

FIG. 3

Case 1. Neoplastic cross-striated muscle elements in the better differentiated areas of the tumour. Heidenhain's Iron Haematoxylin. ×614.

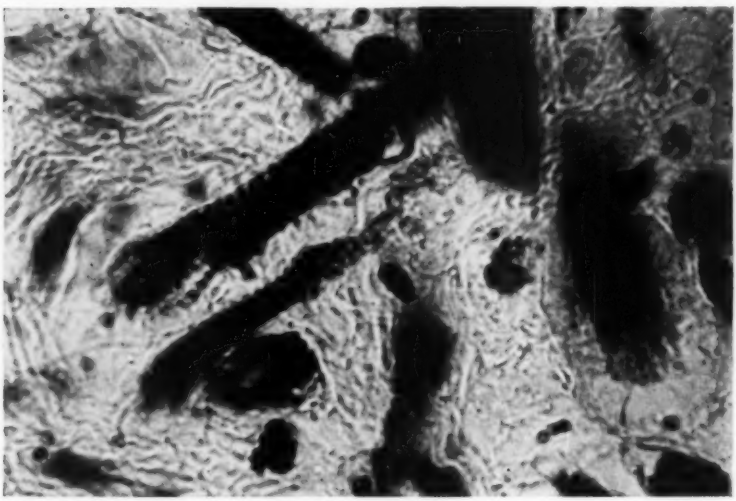

FIG. 4

Case 2. Cross-striated tumour cells from the primary uterine neoplasm. Heidenhain's Iron Haematoxylin. ×614.

spine showed only simple osteoporosis. There was post-climacteric atrophy of both mammary glands.

Microscopical Examination. The uterine tumour was a highly cellular pleomorphic malignant neoplasm. It was not encapsulated and the surrounding myometrial planes were widely infiltrated and disrupted by extending growth which could be followed to the serosa. Three distinct components were recognizable in it. Most of the structure conformed to mixed-cell sarcoma in which variable staining density and grotesque tumour giant-cells were prominent. In some areas the nuclei were closely packed as if in syncytia, in others they were dissociated by oedema. Mitotic figures were very numerous and included many bizarre forms. Dispersed through this basic matrix were many relatively large rounded, fusiform or oblong cells with opaque deeply oxyphile cytoplasm; in a proportion of these, cross-striations were demonstrable by suitable staining (Fig. 4). The final element comprised scattered aggregates of fairly well differentiated fat cells.

In blocks taken from the portion of the neoplasm projecting into the uterine lumen, occasional endometrial glands were found; these showed irritative hyperplasia and were manifestly surviving relics of the membrane which was otherwise overrun by the tumour.

Metastases were confirmed in the peritoneum, diaphragm, lungs and abdominal lymph nodes. They were absent from the liver and kidney. The secondary growths closely mimicked the anaplastic sarcomatous moiety of the primary tumour but were devoid of fat cells, and convincing myoid cells were rare. The tumours of the thyroid gland were adenomata displaying a regular trabecular pattern.

Discussion

The main features of these remarkable tumours in the various sites in which they occur have been well documented, and exhaustive summaries of authenticated cases already exist. These do not require repetition and attention is confined to the pathology of the corporeal variety. When the tumour arises in the body of the uterus the clinical symptoms and signs are not specific. The patient is a post-menopausal woman complaining of abdominal distension or of bleeding and discharge, but bleeding may be restricted or even suppressed because the growth is often surprisingly well covered with intact epithelium, a fact alluded to by many writers. Suspicion of sarcoma is aroused by rapid growth and perhaps by the tumour presenting at the cervical os as an haemorrhagic and friable neoplasm quite unlike the common leiomyoma. Biopsy yields a diagnosis of anaplastic malignant tumour whose morphology is consistent with sarcoma, although its precise affinities may be indeterminate until intensive scrutiny reveals its true nature. Hysterectomy is carried out, followed or preceded by irradiation. It is the usual experience that the patient returns with local recurrence; pelvic extension is the rule in this growth. Spread by the bloodstream is also characteristic, especially to the lungs.

Characteristic naked-eye appearances have been described but are not always present. Shaw discerned a tendency towards arborescence, as in the cervical and vaginal botryoides (i.e., "grape-like cluster") varieties, but this does not seem to be common. The persistence of a more or less intact epithelial covering has already been noted and is also inconstant. The growth arises usually by a pedicle from the fundus and the cut surface shows a mass of tissue of brain-like consistency studded with gelatinous lakes and areas of haemorrhage. The microscopical examination reveals a basic tissue of round or spindle-cell sarcoma, and embedded in this with more or less definition there may be embryonic mesenchyme, striated muscle cells, cartilage, osteoid tissue, bone or fat; and even areas of tissue suggesting tubule or gland formation which have been "mistaken" (Sternberg, Clark and Smith, 1954) for granulosa tissue.

What constitutes a mixed mesenchymal tumour has not been satisfactorily defined, but it is apparently no longer the custom to insist on the demonstration of cross-striated muscle elements. While this may doubtless be a justifiable attitude, our knowledge is still restricted, and it is reasonable to retain the demonstration of striated muscle as unequivocal evidence of a

sarcomatous nature, separating mixed tumour from anaplastic carcinoma.

The cells giving origin to this tumour are undetermined. Remnants of the Wolffian system, Müllerian embryonic cell rests, stromal metaplasia and carcinomatous transformation, have all been suggested as the initium. While provisionally satisfactory on a theoretical basis all lack scientific proof. Willis (1948) dismisses the cell rest theory bluntly: "The supposition that undifferentiated 'rests' of developmentally heterotopic tissues may remain in the endometrium for the whole of a woman's life, surviving multiple pregnancies and eventually produce a mixed embryonic tumour at 50 or 60 or 70, is absurd." The hypothesis is certainly losing favour, but among recent writers Korn (1956) regards Willis's criticism as provoking.

The known plasticity of the cells of the endometrial stroma and their comparative primitiveness render the metaplasia theory attractive, but the premisses for satisfactory inductive reasoning to prove it are still meagre. "Knowledge of cancer origins and behaviour as distinct from knowledge of the behaviour of individual tumour types is nil now . . . as two generations ago" (Lees and Lees, 1952). The mixed mesenchymal tumour along with other partially understood phenomena like endometriosis and pseudomyxoma peritonei must await advances in knowledge before its histogenesis can be other than a guess. It is possible that more tumours than we think are multipotent; if search is continued and especially if all uterine growths are examined with this in mind, the mixed mesenchymal tumour may cease to be a rarity.

Acknowledgments

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TWO UNUSUAL CASES
ECTROMELUS AND OSTEOGENESIS IMPERFECTA

BY

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THE following two comparatively rare cases are presented. They were delivered in the Eastern District Hospital within a few months of each other and raised interesting points in diagnosis and management.

ECTROMELUS

Gould (1939) classifies abnormal development of limbs as follows:

(1) Amelus—A monstrosity without limbs.

(2) Phocomelus—A monster with rudimentary limbs, the hands and feet being attached almost directly to the trunk.

(3) Ectromelus—A single autositic monster characterized by the presence of imperfectly formed limbs.

(4) Hemimelus—A monster with incomplete or stunted extremities.

Poidevin (1953) reported a case of Amelia and reviewed the literature. Posner, Bloch and Green (1957) reported a Phocomelus.

CASE REPORT

Mrs. S.McA., aged 23 years, primigravida, blood group B, Rhesus positive, Wassermann and Kahn reactions negative; last menstrual period commenced on 19th February, 1955; menstrual cycle normal and regular; expected date of delivery 26th November, 1955.

She experienced morning sickness in the early months of pregnancy. Foetal movements were first felt at about five months and continued to be felt till labour commenced.

A breech presentation was diagnosed at the clinic when the patient was 38-weeks pregnant. External cephalic version was unsuccessful despite the help of general anaesthesia. This was considered to be due to insufficient liquor. The pelvis was examined during the anaesthetic and was noted to be normal. No abnormality in the foetus was detected and hospital confinement was booked.

The patient was admitted at 10.15 a.m. on 17th November, 1955, having been in labour for 15 hours. The membranes had been ruptured for one hour. The breech was engaged in the pelvis, the foetal heart was satisfactory and labour was progressing normally. One and a half hours later the breech was showing at the vulva and the usual preparations were made for a primigravid breech delivery.

Until a right postero-lateral episiotomy allowed the complete delivery of the buttocks, it was thought that a normal breech with extended legs was being delivered, but with the delivery of the buttocks, the absence of the lower limbs was noted, the site of their origin being marked by a small button of skin on each side. The patient was anaesthetized as planned. The child's trunk was easily delivered and when the arms were sought so that they could be brought down, it was discovered that they also were absent but for a small segment of the right upper arm. It was then noted that the thin limbless trunk had been delivered through a three-quarters dilated cervix which was preventing the delivery of the after-coming head. Despite firm traction on the trunk, the head could not be delivered and the child succumbed. It was not deemed advisable to do anything further owing to the deformities present.

Owing to the traction, a constriction ring formed at the internal os which could not be relaxed by deepening the anaesthesia, by administering amyl nitrite or by injecting adrenaline. The head was perforated and its size reduced but still delivery could not be achieved. The patient was allowed to recover from the anaesthetic, penicillin was commenced, and pethidine given by injection. The delivery was completed spontaneously 1½ hours later at 2.10 p.m. The patient's puerperium was normal, lactation being suppressed.

The stillborn foetus was 17 inches in length and weighed 4 pounds 4 ounces (Fig. 1). The specimen was preserved and accordingly a modified post-mortem was performed at

Glasgow Royal Maternity and Women's Hospital. This was reported as follows:

"The thorax and abdomen were opened in the midline. The left thorax was almost completely filled with a diaphragmatic hernia containing part of the left lobe of liver, stomach, duodenum, spleen, pancreas, small intestine, ascending and transverse colon. The liver was slightly enlarged and the falciform ligament was deviated to the left. No other significant abnormality was detected in the limited post-mortem examination performed."

X-rays of the foetus were taken (Fig. 2). They show complete absence of limb bones but for a fragment of the right humerus. The shoulder and pelvic girdle bones appear normal but the glenoid cavity appears to be formed only on the side where the portion of humerus is present.

Comment

The patient was well during her pregnancy which was normal but for the breech presentation. The patient's previous health had been good. There was no history of abnormal children in her own or her husband's family. Foetal movements were experienced as expected but since the patient was primigravid she could not compare these movements with those of a normally formed infant. However she later delivered a normal infant on 9th April, 1957 and was under our care during the pregnancy. She stated that the movements she experienced were much more vigorous than those in the first pregnancy.

Even at the time of attempted version under anaesthesia, no abnormality was suspected in the foetus. With a normal pelvis noted at examination under anaesthesia and with no evidence of disproportion, an X-ray examination of the pelvis was not undertaken. No abnormality was detected till the sausage-shaped limbless trunk had been delivered through a three-quarters dilated cervix with retention of the aftercoming head.

Osteogenesis Imperfecta

Vrolik in 1849 described a dystrophy of the foetal skeleton which was characterized by imperfect ossification and abnormal fragility which he termed osteogenesis imperfecta.

Pelner and Cohen (1949) give the following classification of the abnormality.

I. *Foetal Variety*

(1) Stillborn or lives a short time only.

(2) Numerous fractures of ribs and long bones are found.

(3) Skull ossification is incomplete, the skull often being only a membranous bag.

II. *Infantile Variety*

(1) Less severe than foetal type.

(2) May continue for several years, although the prognosis is still poor.

(3) Ossification of cranium incomplete but much further advanced than foetal type.

III. *Osteogenesis Imperfecta, Tarda or Fragilitas Ossium*

(1) Infant is born healthy and may have a normal childhood except for fractures occurring for the slightest cause. These fractures begin at birth or shortly after.

(2) As patient grows older, there is often less tendency for fractures to occur.

(3) Associated findings:
- (*a*) Blue sclerae.
- (*b*) Deafness of otosclerotic type.
- (*c*) Peculiar shape of skull.
- (*d*) Laxity of ligaments.
- (*e*) Abnormalities of teeth and nails.
- (*f*) Shortened length of long bones.

The condition appears to be due primarily to an abnormality of the embryonic mesenchyme, being dominantly inherited with varying degrees of expressivity. The condition may arise as a result of gene-mutation. This was possibly the cause in the case about to be described as there was no family history of any such abnormalities.

Case Report

Mrs. J.R., aged 29 years; para-2, gravida-3; blood group O, Rhesus negative with no antibodies; Wassermann and Kahn reactions negative; last menstrual period commenced on 8th September, 1955; expected date of delivery 15th June, 1956.

FIG. 2
X-ray of ectromelus.

FIG. 1
Ectromelus.

W.F.B.

FIG. 3

Osteogenesis imperfecta *in utero*.

Arrow "A" points to the poorly ossified skull. The other arrows point to some of the many fractures.

(Compare with Fig. 6.)

FIG. 4

Osteogenesis imperfecta at birth.

W.P.B.

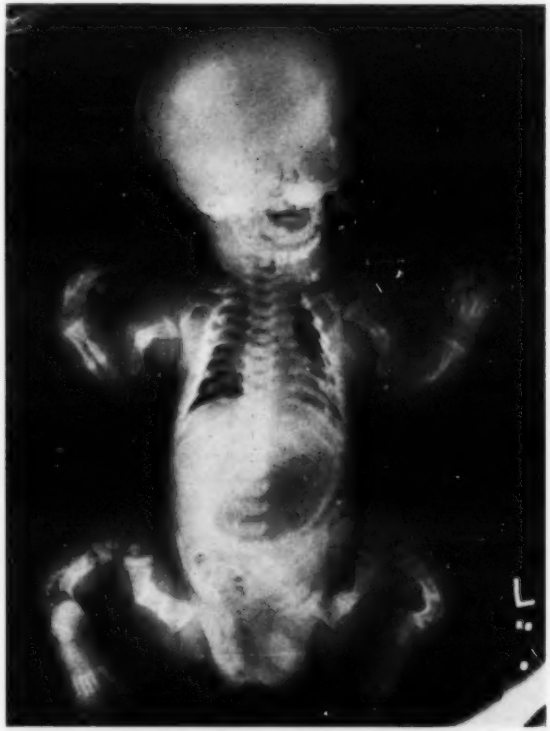

FIG. 5

Osteogenesis imperfecta at birth.

FIG. 6

Achondroplasic foetus *in utero*.

Compare bone density with that of osteogenesis imperfecta. Arrow "A" points to the foetal skull. The other arrows point to the stunted extremities.

The patient's two previous pregnancies were normal. When 12 years of age she had a right mastectomy for a pigmented naevus. Otherwise her previous health had been good. There was no family history of congenital abnormalities or defects.

She first attended the hospital Antenatal Clinic when she was 30-weeks pregnant. Her pregnancy had been progressing normally. On 24th May, 1956, when she was 36-weeks pregnant, a breech presentation was diagnosed and external cephalic version was successfully performed at the clinic. One week later doubt was felt about the presentation of the foetus and her abdomen was X-rayed. The X-ray was reported as follows:

"Single foetus, breech presentation, sacrum left anterior. The size of the foetus suggests a pregnancy of 34 to 36 weeks. The foetus is poorly calcified. Poor definition of the upper limbs is apparently due mainly to osteoporosis. There is fracture of one humerus. The radius and ulna may be short and congenital abnormality of hands and wrists is not excluded. The bones of the lower limbs overlie the maternal sacrum and are not well defined again apparently due to osteoporosis. Some stunting of the bones may be present. At least one of the foetal legs appears flexed. The cranial bones are thin and slight hydrocephalus is suspected. The general appearances are highly suggestive of osteogenesis imperfecta."

It was considered that more informative X-ray pictures could be obtained with the foetus presenting as a vertex whereby the foetal pelvis and lower limbs would lie in the fundus of the uterus and so not be obscured by the maternal sacrum. On 5th June, 1956, external cephalic version was performed at the clinic. Further X-rays were taken (Fig. 3) and were reported as follows:

"The foetus is now in vertex presentation, L.O.A. Slight hydrocephalus is still suspected but the biparietal diameter of the foetal skull is not greater than that of the obstetric conjugate. The bones of the lower limbs are now discernible and show fractures of the femora, tibiae and fibulae. Faint epiphyses for the distal ends of the femora are seen indicating that the pregnancy is nearing full-term."

The patient was admitted to the antenatal ward on 12th June, 1956, when she was near term. The foetus presented as a vertex in the left occipito-lateral position. The head was free. The uterus was enlarged to the size of a 38-weeks pregnancy.

A surgical induction of labour by high posterior rupture of the membranes with a Drew Smythe catheter was performed at 2 p.m. on 19th June, 1956. The pelvis was noted to be normal. The cervix admitted one finger but was not effaced. The foetal head was noted to be soft with wide suture lines and was considered to be hydrocephalic. Fifteen ounces of clear liquor were obtained.

A live lethargic male child (Fig. 4) weighing 5 pounds 3 ounces was delivered at 12.40 a.m. on 23rd June, after a normal labour lasting 3¼ hours. The patient's puerperium was normal, lactation being suppressed.

The infant responded quickly to the usual methods of resuscitation and was transferred to the Premature Nursery. The head appeared larger than normal. The skull bones were very soft and the suture lines wide. The head became flattened on whichever side it lay. Initially the child was thought to be hydrocephalic but this was subsequently disproved. There was gross deformity of all the limbs, due to multiple fractures. The sclerae were not considered to be typically blue. The child was X-rayed shortly after birth (Fig. 5) and the radiograph showed the typical features of osteogenesis imperfecta congenita. A further X-ray was taken on 21st July and this showed callus-formation with healing of the fractures.

The child was Rhesus positive, Coombs negative. Bottle feeding was commenced. The child thrived slowly but satisfactorily. Initially the infant greatly resented handling as would be quite expected with multiple fractures. The nursing care required considerable skill, dexterity and gentleness. An easily reducible right indirect inguinal hernia developed but did not cause any trouble. The child was transferred to the Royal Hospital for Sick Children for further investigation and treatment on 21st July, when his weight was 5 pounds 11 ounces.

The infant was in the Sick Children's Hospital for three weeks. He was slow to thrive. There was considerable difficulty with feeding and constant regurgitation. The baby also had a stubborn respiratory infection. Eventually feeding was stabilized and his general condition improved. He was dismissed home on 12th August. While at home his fractures appeared to improve but the child died when one year old. The cause of death could not be ascertained.

Comment

According to Brailsford (1943) it would appear from a study of radiographs that in the foetal type, except for the cortex of the bone, ossification does not proceed beyond calcification of the cartilage. Consequently the skeleton is unable to withstand the crushing effect of labour and multiple fractures result. In the less severe dystrophy, the infant survives with multiple fractures, flattened vertebral bodies, expanded extremities of the tubular bones with a relative hypoplasia of the shaft and a tendency to ballooning of the thin skull. The histopathology of the condition has been described and discussed by Knaggs (1926) and Aitken, Cohen and Verco (1954).

The differential diagnosis from the radiological aspect for the condition occurring *in utero* is given by Gillanders (1957) as follows:

(1) *Foetal death.* Spalding's sign and the characteristic collapse of the skeleton would be expected before demineralization was sufficiently marked to cause confusion.

(2) *Chondrodystrophy.* The long bones are short and stumpy but demineralization and fractures are not encountered.

(3) *Anencephaly*. Ossification is often heavy. The skull base is malformed and relatively dense. A myelocele is frequently present.

(4) *Achondroplasia*. The long bones are short and broad but the skeleton is normally calcified. No fractures are present. (Figure 6 shows an achondroplasic foetus *in utero*. The infant was delivered in our Unit in 1957. Comparison with the radiographs of the osteogenesis imperfecta foetus shows the difference in bone density and absence of fractures although the extremities are very stunted.)

(5) *Cleido-cranial dysostosis*. The skull vault is poorly calcified; a mosaic of ossification is also found in this condition. The remainder of the skeleton will show a normal calcification density.

(6) *Ectromelia*. Foetal calcification normal.

(7) *Hydrocephalus*. Calcification of the skeleton is normal. The degree of distension of the head is usually marked and a myelocele is often present. In osteogenesis imperfecta, hydrocephalus may be suggested by the apparent thinness and relative enlargement of the cranial vault. Hydrocephalus may, of course, co-exist and should not be assumed in the absence of supporting clinical evidence.

Brailsford (1942) discusses the radiological appearances of the skeleton at birth in normal and abnormal infants. Diagnosis of osteogenesis imperfecta *in utero* has been described by Danelius (1933), Frerking and Zinc (1952), Aitken, Cohen and Verco (1954), and Gillanders (1957). The abnormality was suspected *in utero* and confirmed after delivery by Brailsford (1948) and Hortemo (1953).

Staples and Riva (1954) report cases of maternal osteogenesis imperfecta. In our Unit in 1954 a 25-year-old gravida-2, para-0, was delivered of an apparently normal male child weighing 8 pounds 3 ounces, after a labour lasting 5¾ hours. She had blue sclerae and gave a history of previous multiple fractures. Her father had bony fragility with many fractures. She had 3 brothers and 3 sisters. One brother and 1 sister had blue sclerae and had suffered several fractures. Unfortunately the patient could not be traced.

In the case described, the fractures noted *in utero* were probably caused by external manipulations, particularly the external cephalic versions. Further skeletal damage is likely to have occurred during labour.

The immediate care of the newborn infant is a nursing problem and the further supervision, investigation and treatment of the child a paediatric problem.

Discussion

The cause of these two congenital defects can be considered to lie in some abnormality of the embryonic mesenchyme. Whereas osteogenesis imperfecta is a generalized defect in bone development, ectromelia is manifest by an arrest in development of the limb buds which probably results from some defect in the organizers involved in limb development. Furthermore osteogenesis imperfecta has been firmly established as an hereditary defect although its initial appearance in a family may be due to gene-mutation. Ectromelia, however, owing to its rarity, has been insufficiently studied to justify any firm conclusions as to its origin other than to suggest gene-mutation as a possible factor.

Both cases were diagnosed as breech presentations. This suggests that in breech presentations the possibility of foetal abnormality should be kept in mind particularly with reference to abnormal limb development which however is uncommon. These two rare abnormalities have also to be considered in the differential diagnosis of foetal skeletal deformity as shown by radiological examination in the antenatal period.

Summary

(1) An ectromelus is described and the condition discussed.

The difficulty which may arise with delivery of the aftercoming head in such a case is noted.

(2) A case of osteogenesis imperfecta is described and the condition discussed.

The abnormality was diagnosed *in utero* by radiological investigation.

(3) Common factors in these two rare cases are:

(*a*) A defect in the embryonic mesenchyme in osteogenesis imperfecta which has a strong hereditary background.

(*b*) A possible defect in the embryonic mesenchyme in ectromelia probably associated with a defect in the organizers involved in limb development.

(*c*) Both conditions have to be considered in the differential diagnosis of foetal skeletal defects diagnosed *in utero*.

ACKNOWLEDGMENT

I wish to thank Mr. Hugh Stirling, in whose wards these patients were delivered, for permission to publish this report and for his criticism and advice during its preparation.

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PHAEOCHROMOCYTOMA COMPLICATING PREGNANCY

BY

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SUCH a rare complication of pregnancy is of sufficient interest to be recorded. The number of cases reported is still small, 29 pregnancies in nineteen patients discovered from the literature by Peelen and De Groat (1955) and phaeochromocytoma diagnosed in 85 parous women (Gemmell, 1955).

The tumour was first described by Frankel (1886) and Pincoffs (1929) is accredited as being the first to make the diagnosis pre-operatively and to remove the tumour successfully.

Sudden attacks of headache, anxiety, nervousness, palpitations, dyspnoea, epigastric pain, tachycardia, substernal pain, nausea and vomiting, lasting from a few minutes to several days, characterize the condition. Blacklock *et al.* (1947) described four well-defined clinical groups:

(1) *Adrenal-sympathetic syndrome*—typified by paroxysmal attacks of hypertension due to excessive and intermittent secretion of adrenaline and noradrenaline into the circulation.

(2) *Persistent hypertension*—presenting clinically as either benign or malignant hypertension.

(3) *Asymptomatic*—usually diagnosed post-mortem.

(4) *Malignant group*—The diagnosis is always difficult, there being no well-defined symptom complex; pregnancy may completely mask the symptoms. Pre-eclampsia was diagnosed in half of the cases recorded, mainly on the evidence of headache and hypertension; Gemmell (1955) has pointed out that albuminuria and oedema are usually absent.

Two cases presented as fulminating pre-eclampsia. One patient died undelivered (Hoogeveen, 1948); in the other case, the pregnancy was terminated by Caesarean section, the patient dying of shock a few hours later (Peelen and De Groat, 1955). In both cases the phaeochromocytoma was discovered at post-mortem examination.

A diagnosis of accidental haemorrhage was made in one case; a live baby was delivered by Caesarean section, the patient dying at operation. There was no evidence of accidental haemorrhage (Gemmell, 1955).

CASE REPORT

The patient, aged 26 years, was first seen in October, 1951, when she was 2-months pregnant in her first pregnancy. Apart from childish illnesses the patient had had a tonsillectomy performed in 1947, and a cervical cauterization in 1949. On examination, the patient was found to be normal in every way, blood pressure 120/76, weight 8 stone 5 pounds, urine normal.

A month later she complained of some vomiting and vague epigastric pain. No abnormalities were discovered. The blood pressure was 118/70. The patient was reassured and the symptoms disappeared. Until the 36th week the pregnancy was uneventful, when the patient complained of occasional attacks of palpitations which she noticed particularly when she was lying down. No cause for these attacks was evident; otherwise the pregnancy progressed normally until term. The labour lasted only four hours and was terminated by a low forceps delivery of a living female infant, weighing 8 pounds 10 ounces. During the puerperium the

patient complained of headaches, starting on the fifth day. The blood pressure was not recorded. The puerperium was otherwise uneventful.

In April, 1953, the patient was seen again, still complaining of attacks of palpitation, worse on lying down. At the patient's next visit, in June, 1953, she was found to be 8-weeks pregnant. The blood pressure was 120/70 and she was feeling well.

One month later she again complained of vague episgastric pain, tending to go towards the right iliac fossa; other than this, the pregnancy continued normally until term, labour being terminated by a low forceps delivery of a living male infant of 7 pounds. The puerperium was normal.

When seen in September, 1954, the patient was again 8-weeks pregnant. The blood pressure was 100/76. This pregnancy was absolutely uneventful. Labour started at term and at 7.15 p.m. the cervix was found to be half dilated and she was given 100 mg. of Pethidine by intramuscular injection. Nitrous Oxide, Trilene and Oxygen analgesia was given during the latter part of the first stage and the second stage of labour. At 8.35 p.m. a forceps delivery was performed, the living male infant weighing 7 pounds 9 ounces. Ergometrine 0·5 mg. was given intravenously with the birth of the anterior shoulder. The anaesthetic was discontinued just before the actual birth, only oxygen being administered to assist the baby, which cried immediately. The patient partly regained consciousness and coughed. The third stage of labour was concluded about seven minutes after the birth of the baby.

By this time the patient was almost conscious but continued to cough and began to produce frothy blood-stained mucus. The air passages were cleared with the aid of an electric suction apparatus, but only for a few moments as the frothy fluid began to increase in amount. Atropine gr. 1/100 was given intravenously, the head of the bed was tipped down. An endotracheal tube was passed and a large quantity of the frothy fluid was aspirated. By this time the patient had become deeply cyanosed and was struggling hard to breathe. The pulse was fast and of very poor volume and the temperature was found to be 107° F.

Despite the administration of Coramine, atropine, oxygen and Helium, the patient continued to produce vast amounts of frothy fluid until she died one hour and ten minutes after delivery.

Approximately two pints of frothy blood-stained fluid were aspirated in all. At post-mortem examination, a small phaeochromocytoma three centimetres in diameter was discovered in the right adrenal gland. Death was presumed to have been due to a sudden terrific rise in blood pressure caused by the phaeochromocytoma producing adrenaline and noradrenaline. This produced acute pulmonary oedema due to sudden left-sided heart failure.

Discussion

Hypertensive attacks appear to be initiated by a wide variety of factors; pain, exercise, psychological upsets and minor operative procedures can precipitate the tumour into activity. Graham (1951) reviewed the cause of death in 72 patients, who had a phaeochromocytoma which was not subjected to surgery. He found that 6 patients died suddenly whilst undergoing relatively minor operations; reduction of a fracture, extraction of a tooth, herniorrhaphy, caecostomy for impaction of faeces, and an operation upon the anus. A further 43 of these patients died of a vascular accident, cardiac decompensation or a hypertensive attack. It is of interest to note that 3 patients died at delivery, 2 of them under spinal anaesthesia.

Hyperpyrexia of 107° F. was noted in the case recorded; this finding was also noted by Peelen and De Groat (1955), Jelliffe (1952), and in 7 of the cases discussed by Graham (1951).

Graham (1951) also reviewed 33 operative deaths; 9 patients died of shock during the operation, 13 died within twelve hours of operation, and 6 died within forty-eight hours, nearly all of shock; pulmonary oedema being reported in 3 cases and hyperpyrexia in 3 cases.

Gemmell (1955) has suggested that the activity of the tumour may be related to times of altered endocrine activity; the possibility of endocrine changes associated with pregnancy awakening the phaeochromocytoma into activity cannot be overlooked.

The condition is most often diagnosed during the child-bearing years; frequent examinations performed in the antenatal period, plus the memory of cases such as this one should increase the chance of the diagnosis being made. Even when the diagnosis is suspected, the investigations may prove false, or, even worse still, may themselves initiate a fatal attack of hypertension; 3 such cases were reported by Graham (1951). Mere abdominal palpation or handling of the tumour at operation may produce severe hypertension. Bowen *et al.* (1950) considered that manipulation and movement of their patient in preparation for the night probably precipitated the fatal attack. It is conceivable that uterine contractions and the expulsatory efforts of labour may likewise stimulate the tumour.

Gemmell (1955) found that there was a close time relationship between pregnancy and the making of the diagnosis in 35 out of 115 cases reported in women between the ages of 20 and 50 years. He also noted that the severe symptoms were just as likely to develop during the puerperium as during the pregnancy. Of the 18 cases occurring during the puerperium quoted by Gemmell (1955), only 6 had severe symptoms immediately after delivery; the remainder developed symptoms some hours or days later, showing little or no relation to the state of the uterus. In these cases it is difficult to imagine what the "trigger mechanism" might be.

Approximately half of all recorded maternal deaths are due to shock and haemorrhage. The diagnosis of shock is being made less often. Instead, more tangible conditions such as ruptured uterus, amniotic embolus, afibrinogenaemia and anaesthetic complications are being discovered.

Three adrenal states can bring about "obstetric shock" with serious post-partum collapse and death (Hunt and McConahey, 1953):

(1) Post-partum collapse due to phaeochromocytoma.

(2) Post-partum crisis in women with adrenal insufficiency.

(3) Acute adrenal cortical insufficiency after delivery of patients with induced adrenal cortical atrophy due to previous Cortisone therapy.

The second and third of these states can usually be recognized beforehand but the phaeochromocytoma may quite suddenly become active and be rapidly fatal. Post-partum, the case usually presents as one of severe shock, the true cause only being discovered after death.

Sayer, Moser and Mattingley (1954) recorded a case of severe post-partum shock which did not respond to any therapeutic measures, when recovery occurred spontaneously after twelve hours. A phaeochromocytoma was diagnosed and successfully removed at subsequent operation.

Diagnosis

Clinical examination will rarely reveal the presence of a phaeochromocytoma, likewise X-ray methods including pyelograms and perirenal insufflation may only help when the tumour is a large one, or show on which side the tumour is located when other tests have confirmed the diagnosis.

Estimation of the urinary catecholamines (adrenaline and noradrenaline) is a reliable but difficult method; however, multiple pharmacological tests have been used to make the diagnosis, both "provocative" and "adrenolytic" (Evans *et al.*, 1951). Histamine, metacholine, or tetraethyl-ammonium bromide will all provoke a paroxysm of hypertension should a phaeochromocytoma be present, whereas the adrenolytic drugs, piperoxine, dibenamine, or phentolamine will lower the blood pressure (Bowen *et al.*, 1950; Helps, Robinson and Ross, 1955; Hamilton *et al.*, 1953; Knox and Slessor, 1955).

Unfortunately, both false positive and false negative results occur with most of these tests. However, Goldenberg *et al.* (1954) reported no false results by determining the catecholamines in the urine, using the method of absorption on precipitated aluminium hydroxide plus photofluorometric evaluation.

Treatment

Once the diagnosis has been made, the tumour should be removed. Maloney (1955) and Brann,

Puryear and Landes (1956) have reported cases where the diagnosis was confirmed during the pregnancy, the tumour being removed post-partum; the latter authors consider that Caesarean section should be performed when the foetus is viable, the tumour being removed at a later date.

Handling the tumour at operation may initiate a hypertensive attack which can be controlled with intravenous phentolamine. Once the blood supply to the tumour is cut off and the flow of adrenaline and noradrenaline ceases, the blood pressure may fall precipitously. This can be counteracted by a noradrenaline infusion.

Treatment of an actual "attack" appears to be of no avail; it is unlikely that the diagnosis will be thought of, otherwise phentolamine given soon enough could conceivably be curative.

Comment

In the case described, the attacks of epigastric pain and palpitations complained of in the previous pregnancies were not of sufficient severity to cause any real anxiety. The patient was otherwise extremely well throughout her three pregnancies, there being no evidence of pre-eclampsia at any time.

Previously, the patient had had four anaesthetics with no reaction to the anaesthetic agents; an anaesthetic disaster was discounted at the post-mortem examination.

The size of the tumour bears no relation to the severity of the condition. The weight of the tumour may vary from a few grammes to several pounds (Heriot and Gurling, 1954). Peelen and De Groat (1955) suggest that the average tumour is the size of a lemon. In the case reported by them the tumour was only 6 cm. in diameter, whilst in the fatal case recorded by Bowen *et al.* (1950) the phaeochromocytoma was 5 cm. in diameter. Both these tumours were larger than that in the case that is here described, which had a diameter of only 3 cm.

If diagnosed, the condition is curable, the main limitation being the inability to recognize the condition in the first instance. For the diagnosis to be made more often, the minor symptoms complained of will have to be investigated more thoroughly. When the symptoms are recurrent, and especially when hypertension or pre-eclampsia supervenes, it may be worthwhile considering the possibility of phaeochromocytoma.

Summary

(1) A maternal death caused by a hypertensive crisis due to phaeochromocytoma is described.

(2) The wide variety of the presenting symptoms is discussed.

(3) A closer investigation of hypertension, headache, palpitation, and epigastric pain may lead to the diagnosis of phaeochromocytoma being made more often, especially during pregnancy.

(4) The phaeochromocytoma syndrome occurring post-partum is often indistinguishable from shock due to other obstetric disasters.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of the Council was held in the College House on Saturday, 29th November, 1958, with the President, Professor A. M. Claye, in the Chair.

The *William Blair-Bell Memorial Lectures* for 1959 were awarded to:

Winifred Jean Alexander Francis.

Matthew Lindsay Paterson.

The *Green-Armytage Short-Term Travelling Scholarship* for 1959 was awarded to:

Jeffery Carveth Spry Leverton.

The following have been awarded the **Diploma in Obstetrics:**

Margaret Aitken.
Patricia Mary Akers.
Barbara Anne Alcock.
Kevin Maurice Allman.
Joan Andrews.
John Laurence Andrews.
Hubert Trevor Apsimon.
Albert Edward Ashcroft.
Peter Jervic Ashton.
William Malcolm Baggott.
John Blatchford Ball.
Alan John Barratt.
Dorothy Frances Bate.
David Ernest Robson Bateman.
Michael Arthur Beale.
George Beaumont.
Walter Alexander Beck.
Peter Geoffrey Benson.
George Harry Berry.
Jonathan Francis Bird.
Arthur Booth.
Monica Mary Brain.
Frank Russell Braithwaite.
Edward William Brentnall.
John Frederick Brooks.
Robert Laird Buchanan.
Patricia Mary Bucknole.
James Mervyn Barnett Burn.
Eunice Ruth Burton.
Alan Laurence Bussey.
Margaret Ann Butler.
Leonard Roy Butler-Manuel.
Arthur Richard Robyn Cain.
Pamela Jean Haynes Callaghan.
Peter Fisher Cameron.
Dorothy Catherine Campbell.
William Caplan.
Kamla Chandiramani.
Kenneth Chapman.
Chun Hian Chong.
Ewen Mochrie Clark.
Richard Clark.
Robert William Clark.
Brian Marvin Greenwood Clarke.
Eleanor Mary Clarke.
John Colin Clarke.
John Wilson Clarke.
Alan David Cole.
James Alexander Collie.
Rex Arthur Colwell.
Johanna Connell.
Peter John Constable.
Anna Cope.
John David Corcoran.
Gerald Corney.
Donald Gwynvor Craig.
John Lennox Currie.
John deBerri Johnston Dade.
James Oxenham Dalrymple.
Timothy Patrick Daly.
Ronald John Daniels.
Alan Darnborough.
John Kingsley Dauncey.
Ivan Ethelbert Daunt.
George Albert Davenport.
David Brian Arthur Llewelyn Davies.
Henry William Cecil Davies.
Pamela Anne Deane.
Dhruv Vrat Dhupa.
Donald Graham Dingle.
Piyatissa Dissanayake.
Cynthia Mary Dixon.
St.John Dowling.
Peter Macnaughton Dunn.
Marshall David Leslie Eakin.
Adrian Michael Easty.
Roger William Edmonds.
Brenda Anne Pilcher Edwards.
Norman Anthony Elvin.
Davina Caroline Embleton.

Solomon Ende.
Graham Lees Evans.
Raymond Roker Evans.
David Keith Fairweather.
George William Michael Faris.
John Henry Nelson Ferris.
David Thornton Finlay.
Elizabeth Caroline Finn.
Geoffrey Finnemore.
Francois Louis Pierre Fouin.
Godfrey Heath Fowler.
Archibald Hamilton Frame.
Maurice John Nicolaas Frohn.
Peter Garmon-Jones.
John Norton Garrett.
Susan George.
William Henry Shingler George.
John Harvey Gervis.
Shakuntala Manhar Gheewala.
Jennifer Mary Doidge Gibson.
William Oates Goldthorp.
Dulcie Augusta Fonseka Goonewardena.
Robert Livingstone Grant.
Robert Dickson Gray.
Roderick Ian Graymore.
Ian Gregg.
Aloka Gupta.
Digby William Hall.
Ursula Helena Hamilton.
Hugh William Irvine Hanan.
Susan Elizabeth Ann Hart.
Alexander Haskell.
Tim David Haskins.
Abubakr Mustapha Hassim.
Michael Joseph Herlihy.
Frank Heyes.
Michael David Hickman.
Neville Arthur Hiley.
Jennifer Hill.
Pamela Margaret Hogg.
Malcolm Francis Holding.
Aina Jautrite Holt.
John Homi.
Rachel Shirley Lloyd Hood.
Christopher Vernon Horn.
Frank Horsfield.
Benedict Leigh Hoskyns.
Nigel Ravenscroft Houlston.
James Kenneth Houston.
Brian George Howarth.
Hugh James Hoyland.
Peter John Egerton Hubbard.
Christopher Neville Hudson.
David Ifan Hughes-Davies.
David Hull.
Roy Mackenzie Humble.
James Miller Hutchison.
David Cecil Hutfield.
Reginald Hopkin Huzzey.
Christine Moira Hyslop.
Nalini Mahadeo Inamdar.
George Anthony Irving.
Elizabeth Juliet Ives.
Peter Neville Jarvis.
Hilda Jayawardena.
Brian Lees Johnson.
Denzil Stockton Jones.
Gwendolyn Anne Jones.
John Kenneth Lloyd Jones.
Margaret Jones.
Anusuya Kalyanaraman.
Russell Keeley.
John Common Kennedy Smith.
Michael Gerard Kielty.
Norman Drean Kilpatrick.
Harold Anthony Patrick King.
Richard Glanville Pearson King.
Ronald Arthur Lacey.
Rex Desmond Last.
Arthur Ronald Lea.
Shirley Anne Leslie.
Jon Walford Lewis.
Patricia Alice Charlotte Locken.
John Anthony Lofting.
Basil Edmund Lomax.
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Aileen Campbell Munro.
Duncan Sutherland Munro.
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Nora Millicent Norris.
Terence Dennis Nundy.
Alan Francis O'Grady.
Olusola Adewole Ojo.
Desmond James O'Shaughnessy.
Jean Bronwen Owens.
Sisir Kumar Panja.
Martin Edwin Parry.
Donald George Paskin.
Rajnikant Ishwarbhai Patel.
Walter Gouinlock Paterson.
Ronald Sidney Peachey.
John Frederick Perren.
Geoffrey David Phillips.
Gordon Phillips.
Hazel Mary Phillips.
Samuel Graham Phillips.
Anthony John Platts.

Michael Robert Kirby Plaxton.
Ann Maureen Pocock.
Colin Ross Porteous.
Glynn Priddle.
Saroja Ramaswamy.
Dorothy Elizabeth Robb.
Iorwerth Roberts.
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Shirley Blyth Robertson.
Jayatissa Nalin Rodrigo.
Philip Stewart Rolland.
Ian Gordon Ross.
Abha Rani Roy.
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Palepu Savithri.
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Travers Drewery Sayer.
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Amhmed Abu-el-Futuh Shandall.
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Michael Anthony Shields.
Michael Shillito.
Yehouda Shirazi.
Malcolm Westmoreland Sleight.
William Duncan Smith.
Shirley Margaret Snead.
Kenneth Gordon Ross Somer.
David Moses Sopher.
Stanley Paule Spiers.
John Highet Stewart.
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Sushil Kumar Suppal.
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Andrew Norman Watson.
Gillian Anne Watson.
Douglas Arthur Lawrence Watt.
Ian Watts.
Paul Wellings.
Humphrey James Oakley White.
Deric Haydn Williams.
Peter Wolstencroft.
Clifford Desmond Wooding.
Samuel John Peter Woods.
Thomas Kenneth William Wollacott.
Philip Nigel Wormald.
Arie Jeremy Zuckerman.

The following were admitted to the **Membership:**

Gouri Sankar Mandal.
Ajit Kumar Sarkar.

Congratulations were sent to Professor J. M. Munro Kerr on the occasion of his attaining his 90th birthday anniversary on 5th December.

FIFTEENTH BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

CARDIFF

14TH, 15TH AND 16TH JULY, 1959

THE scientific meetings will be held in the Reardon Smith Lecture Theatre, Cardiff.

Tuesday, 14th July

Opening of the Congress by Sir William Fletcher Shaw.

A Symposium—REMOTE EFFECTS OF OBSTETRICAL HAZARDS ON THE DEVELOPMENT OF THE CHILD

This whole day symposium will be opened by Dr. Duncan Reid, Boston, and among the contributors will be Dr. Alice Stewart, Oxford; Professor Shedden-Adam, Brisbane; Dr. Cecil Drillien, Edinburgh; Dr. Mark Fraser, Aberdeen.

Wednesday, 15th July

PSYCHOSOMATIC GYNAECOLOGY

Opening speakers: Dr. Desmond O'Neill, London; Dr. W. Johnstone, Melbourne; Dr. Elinor Black, Winnipeg.

OESTROGEN METABOLISM

Opening speakers: Sir Charles Dodds, London; Dr. J. B. Brown, Edinburgh; Professor Robert Kellar, Edinburgh; Dr. G. I. M. Swyer, London.

Thursday, 16th July

DEGREES OF MALIGNANCY IN OVARIAN CARCINOMA

Guest Lecture: Dr. Howard Taylor, New York.

THE CONTRIBUTION OF RADIOTHERAPY TO THE MODERN TREATMENT OF MALIGNANT DISEASE OF THE FEMALE GENITAL TRACT

Opening speakers: Professor B. W. Windeyer, London; Dr. W. G. Cosbie, Toronto.

THE PLACE OF OXYTOCIC DRUGS BEFORE THE BIRTH OF THE CHILD

Opening speakers: Mr. A. J. Wrigley, London; Mr. G. W. Theobald, Bradford; Professor Chassar Moir, Oxford; Professor W. C. W. Nixon, London.

A full social programme has also been arranged for members and their ladies.

Membership fees are:

Full Membership	£4 4s. 0d.
Full Day Membership	£1 10s. 0d.
Associate Membership	£2 2s. 0d.
Associate Day Membership	15s. 0d.

Full membership is open to all medical practitioners. Associate membership is reserved for registrars and house officers and entitles them to attend the scientific meetings only.

Fuller details of the Congress and application forms are available from the Honorary Secretaries, Fifteenth British Congress, The Maternity Hospital, Glossop Terrace, Cardiff.

RULES GOVERNING THE AWARD

OF

"THE FOUNDATION PRIZE"

OF THE

AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

1. The award which shall be known as "The Foundation Prize" shall consist of $500.00.

2. Eligible contestants shall include only (*a*) interns, residents or graduate students in obstetrics and gynaecology, and (*b*) persons with an M.D. degree, or a scientific degree approved by the Prize Award Committee, who are actively practising or teaching obstetrics, gynaecology, or engaged in research in these fields. No fellow of the Association shall be eligible to compete for this prize, and no candidate securing the award shall be eligible to compete again.

3. Manuscripts must be presented under a *nom de plume*, which shall in no way indicate the author's identity, to the President of the Foundation together with a sealed envelope bearing the *non de plume* and containing a card showing the name and address of the contestant.

4. Manuscripts must be limited to 5,000 words, and must be typewritten in double-spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

5. The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the official Journal of the Association or, failing that, in a journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors.

6. Three copies of all manuscripts and illustrations entered in a given year must be in the hands of Jean Paul Pratt, M.D., Henry Ford Hospital, Detroit, Michigan, President of the Foundation, before 1st April, 1959.

7. The award will be made at the Annual Meeting of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific programme, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

8. The President of the American Association of Obstetricians and Gynecologists Foundation, Inc., shall annually appoint a Committee on Award, which, under its own regulations, shall determine the successful contestant and shall inform the Secretary of his name and address by 15th May, 1959.

Inquiries for further details should be addressed to the Secretary, E. Stewart Taylor, M.D., University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, Colorado.

12th November, 1958.

REPORTS OF SOCIETIES

GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

March 1957

A Meeting of the Glasgow Obstetrical and Gynaecological Society was held in the Royal Faculty of Physicians and Surgeons, Glasgow, on Wednesday, 20th March, 1957. The President, Dr. D. F. Anderson, occupied the Chair.

Dr. Wallace Barr addressed the Society on

Heartburn in Pregnancy

In his opening remarks, Dr. Barr emphasized that heartburn is probably the most common of the minor disorders of pregnancy but, being a non-fatal condition and never a serious threat to health, it had attracted remarkably little scientific curiosity and controlled experimental work on the subject was virtually non-existent.

The most widely quoted article was that of Williams who in 1941 introduced, as a form of therapy, subcutaneously administered prostigmine and, while it would appear that he had a rational basis for so doing, he brought forward to support his argument a clinical series of only 16 cases. Five years later Wiley (1946) suggested that prostigmine was equally effective when administered orally and claimed a cure in 15 of 20 cases. Other investigations by Rodway and Shelley (1935), Raynor (1932), Braun, Bromberg and Brzezinski (1945) and Kruger (1953) were described and these, together with some relevant work on hiatus hernia, constituted most of the investigations on this subject.

Dr. Barr went on to point out that a confusing factor was the difficulty in accurately defining heartburn. There seemed to be two sets of symptoms:

(1) An indefinite hot or burning sensation (without pain) commonly located in the lower sternum or upper epigastrium often radiating upwards to the angles of the jaw and associated with acid regurgitation.

(2) A definite pain of stretching or distending type situated at the lower end of the oesophagus and associated with a tendency to swallow air or gasp or belch or to thump the affected area to obtain relief.

Dr. Barr then presented his results from a series of 624 cases in the Eastern District Hospital, Glasgow. The following facts emerged:

(1) The time of onset was most commonly between the 12th and 24th weeks of pregnancy.

(2) Age, parity and previous digestive trouble were not significant factors.

(3) In 65·4 per cent of patients the heartburn was worst when lying in bed at night. Including bending, kneeling or lying down, no fewer than 92·3 per cent of cases related their heartburn to posture.

(4) In 33·6 per cent of cases eating was a direct provocation to the onset of an attack of heartburn. The nature of the food varied enormously.

(5) The condition was peculiar to pregnancy and, in all cases, evacuation of the uterus was attended by complete cure within a few hours.

The aetiology of the condition was then discussed in some detail and the possible causes dealt with as follows:

(1) Relationship to gastric acid secretion.

(2) Vitamin B_6 deficiency.

(3) Dietary and functional factors.

(4) Hiatus hernia.

(5) The mechanical effect of the gravid uterus on the position of the stomach.

(6) Oesophageal reflex.

Dr. Barr then presented the results of X-ray screening of 85 cases of heartburn during and after barium swallow. Oesophageal reflex was demonstrated in 64 of them. Gastric motility in pregnancy was then considered in association with heartburn. The method used in this investigation consisted of passing into the stomach a small balloon connected with a tambour transmitting pressure changes to a recording drum. The limitations of the method were recognized. From the findings obtained in a series of 42 cases it would appear that, in the pregnant woman with heartburn, there is a noticeable diminution in tonus rhythm but gastric contractions are unaltered in size or frequency.

Treatment of the condition was then described and the relative value of alkalies, diet, prostigmine and neostigmine hydrobromide were brought forward in turn. Dr. Barr stated that he had been using an oral preparation of acetylcholine with some success. There seemed, however, to be a group of cases which were quite unresponsive to treatment of any kind but which cleared up spontaneously and immediately on the day of delivery.

In conclusion, the speaker indicated that a great deal of experimental work remained to be done. Acknowledgment was made to the generous assistance and advice given by Mr. A. W. Kay and Mr. D. H. Clark of the Western Infirmary and to Dr. Hugh Stirling of the Eastern District Hospital in whose wards Dr. Barr had carried out his investigations.

GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

MAY 1958

A Meeting of the Glasgow Obstetrical and Gynaecological Society was held in the rooms of the Royal Faculty of Physicians and Surgeons, Glasgow, on Wednesday, 21st May, 1958, at 7.30 p.m. The President, Professor D. F. Anderson was in the Chair.

Dr. A. D. McIntosh addressed the Society on

ECTOPIC PREGNANCY AND TUBERCULOUS SALPINX ITS

He said that the occurrence of tubal or ectopic pregnancy in cases of tuberculous salpingitis was relatively rare and only a small number of cases had been recorded in the literature. Most of these reports had been of one or two cases but recently there had been reports of larger numbers of cases of ectopic pregnancy occurring after the treatment of genital tuberculosis. Three cases which occurred in the gynaecological unit in Hairmyres Hospital formed the basis of his short paper.

The histories of the three cases were then described and compared. Two cases had previously been investigated for sterility, and one had been found to have tuberculous endometritis. The presenting symptoms were of interest in that 2 of the 3 patients had previously been admitted to surgical units as possible cases of appendicitis. The operative findings and pathology reports were then discussed and compared and several histological sections shown.

The speaker pointed out the difficulties in both clinical and histological diagnosis and stressed the importance of always considering the association of these conditions in cases of ectopic pregnancy. From recent publications it seemed fairly obvious that the combination of these two conditions was becoming more common and that there was definitely an increased risk of extra-uterine pregnancy after the treatment of genital tuberculosis. Further the occurrence of a second ectopic pregnancy in such cases had also been reported.

In conclusion it seemed reasonable to suggest that in cases of ruptured ectopic pregnancy in patients who were known to have had genital tuberculosis the operation of choice was bilateral salpingectomy.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

JUNE 1958

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Newcastle on 13th June, 1958. The President, Dr. E. A. Gerrard, took the Chair.

Mr. F. Stabler reported a case of

A NAEGELE TYPE PELVIS

The patient presented in her first pregnancy and nothing unusual was noticed until, at the 34th week, the foetal head still being high above the pelvic brim, a vaginal examination revealed marked transverse contraction of the pelvis. X-ray pictures showed all the features of a Naegele pelvis, except that there was a joint space on the affected side.

Naegele in his monograph laid down 6 requirements:

(1) Fusion of one sacro-iliac joint.

(2) Absence or improper development of one-half of the sacrum.

(3) Diminished breadth of the hip bone and sciatic notch on the same side.

(4) The sacrum pushed to the ankylosed side and the pubic symphysis displaced to the opposite side.

(5) The ankylosed side shows flattening of the lateral pelvic wall.

(6) The other side of the pelvis is no bigger than normal.

In Mr. Stabler's case the 1st sacral vertebra is small, deformed and round, and below it an indeterminate mass representing the rest of the sacrum shows two pieces of bone directed horizontally backwards. The patient was delivered by Caesarean section in both this and a subsequent pregnancy. A cardiac murmur was also detected which it was thought represented a septal defect.

Naegele published his monograph in 1839. He saw one patient, who, after delivering a dead child, died of puerperal fever, but he was able to collect details of 37 other cases including the pelvis of an Egyptian mummy. He discussed the difficulty in diagnosis, the usual need for Caesarean section, and said that the deformity was due to a congenital failure of normal development.

Discussion

The President thanked Mr. Stabler for his description of this unique type of pelvis. In the old days it would have been called the Stabler pelvis.

Mr. L. Snaith asked if there was any history of a sacral tumour.

Professor H. H. Evers thought the deformity might have been felt at the time of Caesarean section.

Mr. W. Hunter enquired if a spina bifida was present, and Mr. D. C. Galloway if there was any family history.

In his reply Mr. Stabler said there was no neurological abnormality, the deformity could readily be felt at the time of the Caesarean section, there was no spina bifida, and it would be interesting to X-ray the children.

Mr. H. R. Arthur described a case of

OXYURIS GRANULOMATA OF THE FALLOPIAN TUBE AND PERITONEAL SURFACE OF AN OVARIAN CYST

(This article appears on page 996 of this issue)

Discussion

Miss E. Mills asked if the appendix showed any signs of oxyuriasis.

Mr. F. Stabler thought the husband might be the infecting agent as he did not believe otherwise the acid barrier of the vagina could be passed.

Mr. W. Hunter postulated that the infection had occurred at the time of menstruation and Professor Evers suggested the puerperium.

Mr. H. Doberman enquired how this condition could be distinguished macroscopically from tuberculosis.

Mr. C. Rutherford Morison asked how long the ova lived.

In reply Dr. Tomlinson said that 3 faecal samples and 3 anal swabs had all been negative. The infection might have arisen at or just after menstruation. In this case the tubal fimbriae were normal. Usually ova survive only a few days but may be preserved in arrested development.

Dr. W. Calvert read a paper on

PROGRESS IN THE TREATMENT OF STRESS INCONTINENCE

Mr. Calvert became interested in the problem of stress incontinence when, in 1944, he found the operation for prolapse did not always afford relief. One early case of stress incontinence had already had a Manchester repair. A urethroplasty, extending the anterior colporrhaphy, was successful.

By 1947 Mr. Calvert had found this modified anterior colporrhaphy did not always produce cure, and, following Marshall's example, he carried out a suburethral fascial sling using a free graft from the abdominal wall. The next patient had a stormy but eventually complete recovery.

The first 5 cases so treated went well, but later there was trouble in separating urethra from vagina, and in 3 cases the bladder was ruptured, though this was easily repaired. In some cases the vagina can readily be freed from the urethra, but in others it is detached only with scissors. In this latter type of case a procedure described by Everard Williams in 1950 was performed.

It was possible that the mind played some part in the results, and from 1950 Mr. Calvert began to operate for stress incontinence at the time of some different procedure, and without the patient's knowledge. All but one patient obtained relief.

Later, he placed sutures lateral to the bladder neck without knowing this was the Marshall-Marchetti operation, and, more recently, there have been modifications to the use of the fascial bodkin for the sling operation. This last operation is now considered the operation of choice.

If the patient has marked prolapse and stress incontinence the elective treatment is a Manchester operation. If she has a condition producing severe stress, such as a chronic cough, an Aldridge's operation should be added to the routine repair.

Mr. Calvert placed his patients in four categories defined by the clinical features, and varied his treatment according to the category.

Discussion

Mr. F. Stabler had suggested 10 years ago at the British Congress that, if the urethra was placed against the pubis and held in that position, damage to surrounding tissue would result in fibrosis and cure of symptoms. It did not matter if the splinting material was nylon or the patient's fascia. He did not agree with the supra-pubic approach only as it was difficult to assess the amount of tension required, and he believed the objection to the Aldridge operation on the grounds of infection "did not hold water". The success in the cases where the bladder was accidentally opened was due to the resultant fibrosis, and in some instances where the Marshall-Marchetti operation failed there had been too little fibrosis.

Mr. W. Hunter agreed with Mr. Stabler. He always enquired about the daily fluid intake and highly seasoned foods.

Mr. H. R. Arthur's experience in treating stress incontinence had closely followed Dr. Calvert's. He considered the Aldridge operation too elaborate, and thought a vertical incision and strip of rectus sheath fascia the best as in the Studdiford operation. Damage to the bladder if repaired need not cause concern.

Mr. M. S. Williamson asked about the value of pelvic floor exercises.

Mr. H. Agar had found trouble when the fascial graft surrounded the urethra as in the Millin operation, but not when it was placed as a simple sling in the shape of a U.

Professor H. H. Evers stressed the importance of the follow-up in assessing cure, and asked about stress incontinence developing after a repair operation.

Dr. D. Keith reported a case of urethro-vaginal fistula developing 5 years after an Aldridge operation.

In reply, Dr. Calvert said that he had not found it difficult to judge the necessary tension with the supra-pubic approach. If the graft cut across the urethra it was because the graft was too thin or became twisted. Usually no difficulty was encountered in re-inserting the catheter. Exercises were of value only in the first 3 months after delivery. He had seen stress incontinence develop after a repair operation and thought it important to carry out suburethral anterior colporrhaphy in all cases to avoid this.

BOOK REVIEWS

"Annual Report on the Results of Treatment in Carcinoma of the Uterus." Eleventh Volume. Stockholm, 1958. Statements of Results obtained in 1951 and previous years.

IN the present, 11th Report statements on carcinoma of the cervix are contributed by 86 institutions, 79 of which also collaborated in the 10th Report. The submitted statements on carcinoma of the cervix cover 129,396 cases from 22 different countries. As in the previous years the aims of the Report are to establish rules for the presentation of therapeutic cancer statistics and to ensure a proper understanding of the importance of recording all cases in a uniform way. In the present volume particular emphasis has been given to the special figures relating to individual institutions, the purpose being to provide information concerning the organization of the collaborating institutions and the material presented by them. The combined tables are presented in a condensed form excluding separate statements giving figures for individual years. Whereas in the last 4 Reports statements on carcinoma of the cervix Stage 0 had been included, the Editors of the present Report did not think it advisable to admit Carcinoma Stage 0 because of the prevailing differences of opinion regarding the nature of this lesion.

Of the 129,396 patients with carcinoma of the cervix 120,738 (93·3 per cent) were treated. The overall relative apparent recovery rate including all years reported on showed considerable improvement to previous figures, being 37·3 per cent as compared to 35·3 per cent in Volume 10 and 34·7 per cent in Volume 9. Corresponding figures for the latest 5 years are 42·8 per cent in the present survey as compared to 39·8 per cent in Volume 10 and 38·3 per cent in Volume 9. It appears from the detailed studies of the figures submitted that this improvement in therapeutic results is not due to additional material from new collaborators. There seems to be a slight improvement in the quality of the clinical material but the chief factor in the better results obtained is an increase in apparent recovery rates.

Data relating to carcinoma of the corpus were submitted by 29 collaborators relating to a total of 11,722 cases of which 11,291 (96·3 per cent) were treated. The overall apparent recovery rate of 56·5 per cent in the Report is the highest yet presented in the series, the comparative rates being 54·3 per cent in Volume 10, 53·0 per cent in Volume 9 and 52·4 per cent in Volume 8. This improvement seems to be due both to the changes in the quality of the material and to changes in the recovery rates.

The present volume continues the excellent work begun by the late Professor James Heyman in 1937 and much admiration is due to the new Editors for the clear and lucid presentation of such a complex and varied material.

Erica Wachtel

"Textbook for Midwives." By MARGARET F. MYLES, S.R.N., S.C.M., H.V.Cert., M.T.D. Third edition. Pp. xii+711, with 392 figures. E. & S. Livingstone, Edinburgh and London, 1958. Price 42*s*.

"Textbook of Obstetrics and Obstetric Nursing." By MAE M. BOOKMILLER, R.N., and G. L. BOWEN, A.B., M.D., Bellevue Hospital, New York. Third edition. Pp. xx+725, with 372 figures. W. B. Saunders, Philadelphia and New York, 1958. Price 42*s*.

THESE two books afford a comparison of both medical and nursing practice in obstetrics on opposite sides of the Atlantic. They are the same reasonable price and of the same page-length, but whereas the print from the U.S. is uniform in type, the British book has three sizes of print—average, small and juxta-microscopic.

The first edition of Mrs. Myles' work was published as recently as 1953 but her textbook has already become a "classic" in its field, and not surprisingly so because it is almost encyclopaedic. It is difficult to believe that there is anyone practising obstetrics, from the medical student to the consultant, who could not profit from reading the new edition. Throughout the text, which is remarkably up-to-date, not only are all practical measures carefully detailed but theoretical considerations are also adequately aired and with a fine sense of balance. The section on mothercraft teaching includes actual talks as the midwife should give them to the patient and as the doctor might also profitably retail them.

The textbook by Miss Bookmiller and Dr. Bowen is more discursive, probably because there is no statutory body in the U.S.A. comparable to the C.M.B. here. It may also be that the obstetric nurse in the U.S. has to cope with a wider range of procedures, for example in analgesia in labour. The text, which opens with a commendable chapter on the history of obstetrics and obstetric nursing, is easy to read, well-illustrated and accompanied, unlike its British counterpart, by selected references. And who would have expected that the chapter on confinement in the home would be longer in the transatlantic book?

"Obstetric Operations—Techniques and Indications. (Die Geburtshilflichen Operationen—Ihre Ausführung und Anwendung.)" By Prof. Dr. med. HEINRICH MARTIUS. 8th Edition. Pp. xvi+281, with 253 figures. Georg Thieme, Stuttgart, 1957. Price D.M. 29.60.

THE latest edition of Professor Martius' book is a shorter and more concise version of the previous editions. No new developments have occurred in the field of Obstetric Surgery in the last 5 years since the 7th edition was published and, for that reason, no new chapters have been added to the book. Spectacular advances have been

made by the pharmaceutical industry in recent years but, although these new drugs have their place in obstetrics and greatly enhance the safety of surgical procedures, they have not materially influenced the indications for obstetric surgery. However, with the advent of these new drugs and greater safety in abdominal surgery, a number of previously advocated procedures are becoming more and more obsolete. Less space than in previous editions has been allocated to these procedures which include anterior vaginal hysterotomy, embryotomies, high forceps, etc., but their description remains clear-cut and adequate.

Although much time is devoted to the chapter on the management of spontaneous abortions and a new vacuum extractor is described in detail, we miss with regret the mention of the one recent surgical attempt at prophylaxis of habitual abortions, viz., the Shirodkar operation. This, however, is the only criticism we have to offer.

Professor Martius is a master in the art of teaching. His textbook with its exquisite drawings is a vivid proof that the teaching of surgery need not necessarily be confined to bedside and theatre but can also be given by the printed word and illustrations. It seems a pity that no English translation of this standard textbook is available.

"Pediatric Gynecology." By GOODRICH C. SCHAUFFLER, M.D. Fourth edition. Pp. 349, with 84 illustrations. The Year Book Publishers, Chicago, 1958. Price 57*s*.

DURING the post-war era many minor branches of medical science have blossomed into full maturity. This book, now in its fourth edition, is a brave attempt to establish the study of the gynaecological aspects of immature females as a separate subject in its own right. The author draws on a wide experience in presenting a practical approach to the clinical management of these children. A panel of experts assisted in the preparation of interesting chapters on general surgical aspects, urology, proctology, social services and medico-legal problems. The remainder of the text is particularly concerned with the moral and social problems which accrue from "the hysterical all-American pre-occupation with sex ———", with its trail of precocious and amoral practices, and serves as a timely warning to the British parent who is tempted to relax the traditionally strict but sympathetic parental discipline.

"Abortion in the United States." Edited by MARY STEICHEN CALDERONE, M.D. Cassell & Co. Ltd., London, 1958. Price 42*s*.

THIS is a report of a Conference sponsored by the Planned Parenthood Federation of America in April, 1955. Forty invited participants, including many names well known in this country, met for six 3-hour sessions to discuss illegal and therapeutic abortion, and again two months later most of them met again for a whole day. The excellent editing of six hundred pages to produce this very readable report of only two hundred pages calls for praise, admiration and gratitude. Ranging from abortion in Scandinavian countries to the legal aspects of abortion in the United States, and including psychiatric and sociologic aspects and the relationship of abortion and contraception, the subject appears to have been thoroughly and honestly discussed in human terms. It is fascinating to read and cannot but help to educate and enlighten all who deal with this problem continually in their clinical work. A great deal of the report is still written as a discussion, with questions put to speakers, and no outline of any brevity is possible. A statistical committee attempts the unenviable task of estimating the incidence of illegal abortion and is forced to conclude that it might be as low as 200,000 per annum, or as high as 1,200,000. A "Statement" summarizes the opinion of the conference along five advocated directions in order to reduce illegal abortion. First, further and extensive studies of all aspects of the problem, to be sponsored by Foundations and Government bodies. Second, the setting up of consultation centres for women seeking abortion modelled on the existing Scandinavian centres and these to operate under joint medical and sociological auspices through the sponsorship of state health and welfare departments. Third, extension of facilities for advice on contraception, although the conference found no scientific evidence to support the notion that this would definitely lower the abortion rate. (They "deplore the inequality of availability of legal abortion as well as contraceptive information, both of which are more readily available to the educated and financially privileged".) Fourth, encouragement of intensive sex education, to encourage a greater sense of responsibility toward pregnancy. Fifth, study by law commissions with a view to unifying abortion laws over the forty-eight states, and to recognize the mounting approval of psychiatric, humanitarian and eugenic indications for the legal termination of pregnancy, in the light of the fact that almost no therapeutic abortions performed today are legal, since with the improvement of modern medicine it rarely becomes necessary to perform an abortion to save life. The English case of Rex versus Bourne is mentioned in the discussions and Judge McNaughtan's deliberations are afforded two pages, in an appendix.

Altogether a worth-while two guinea investment.

"Obstetrics and Gynecology." By J. ROBERT WILLSON, CLAYTON T. BEECHAM, ISADOR FORMAN and ELSIE REID CARRINGTON. Pp. 605, with 267 illustrations. Henry Kimpton, London, 1958. Price 80*s*.

THIS textbook from Philadelphia is designed for medical students and family doctors. For the former it provides a sound foundation, while to the latter it states clearly those conditions under which they should seek consultation with a specialist. Gynaecology and obstetrics are correctly treated as one integrated branch of medicine, with reproduction and its disorders relevant to the child-bearing years of the life-history of woman. The length of the book has been kept within reasonable bounds by omitting basic anatomy and details of operative procedures. Altogether, the authors, the senior of whom is responsible for almost half of the chapters, have

succeeded in their object of producing something more than a synopsis and something less than an encyclopaedic text. One foresees that the popularity of this textbook will extend beyond the Temple University Medical School from which it originates.

"Essentials of Gynecology." By E. STEWART TAYLOR, Professor of Obstetrics and Gynecology, University of Colorado, Denver. Pp. 502, with 343 illustrations, 4 in colour. Henry Kimpton, London, 1958. Price 84*s*.

THIS is a new book, prepared for medical students and recent graduates, in which malignant disease and endocrinological aspects are especially stressed. The inclusion of chapters on the adrenal, pituitary and thyroid glands in relation to gynaecology is to be welcomed, but it is doubtful whether it is advantageous to present operative details in a book of this calibre. Emphasis is laid on prevention and on early diagnosis, and women are advised to seek physical examination every year until 40 years old and then every 6 months. The illustrations, many of them borrowed, are good and the photomicrographs are of a high standard, but the proofreading has not been faultless (e.g., "pruritis", "pyrometrium"). A chapter on symptomatology would add to the virtues of the book, but faith in its text is diminished by a few such statements as: "the period of irregular or abnormal menstrual function leading to the menopause is called the climacteric."

"Human Parturition—Normal and Abnormal Labor." By NORMAN F. MILLER, M.D., F.A.C.S., A.C.O.G., T. N. EVANS, M.D., F.A.C.S., A.C.O.G., and R. L. HAAS, M.D., F.A.C.S., A.C.O.G. Pp. 248, with 66 illustrations. Baillière, Tindall and Cox, London, 1958. Price 60*s*.

THIS slim book from the University of Michigan Medical School is intended primarily to provide the medical student with a foundation on which to build clinical experience. It deals mainly with but one sector of obstetrics, namely, normal and abnormal labour, but ante-partum haemorrhage and abortion are also included. The text, which is for the most part in tabulated form, is orthodox, concise and up to date. The student in this country will find that some definitions (e.g., of presentation and crowning) and some practices (e.g., a greater frequency of vaginal or rectal examinations in the second stage) are different from what he is taught here. And he is likely to regard £3 as a very high price to pay for an "Aids" to part of one subject.

THE NUFFIELD FOUNDATION
NUFFIELD INSTITUTE FOR MEDICAL RESEARCH

RESEARCH FELLOWSHIPS

THE Nuffield Foundation, as an experiment, is prepared to offer one research fellowship annually in each of the three years 1958, 1959 and 1960, tenable at the Nuffield Institute for Medical Research at Oxford, to enable a suitably qualified person who intends to follow an academic career in obstetrics or paediatrics in the United Kingdom to concentrate for a year on animal experiments directly related to basic physiology or pharmacology in the foetus or the newborn.

Each fellowship will be tenable for one year and is limited to a graduate in medicine of a University within the British Commonwealth, who should *either* have completed an appointment as Registrar (or its equivalent) in an approved department of obstetrics or paediatrics, *or* be seconded for one year from such an appointment. He should also have obtained the higher qualification appropriate to his chosen speciality. The stipend will be within the approved range of salaries for Senior Registrars under the National Health Service. Applications for the award beginning in 1959 must be received before 15th February, 1959, by the Director, The Nuffield Foundation, Nuffield Lodge, Regent's Park, N.W.1, from whom full particulars and application forms can be obtained.

L. FARRER-BROWN,
Director of the Nuffield Foundation.

REVIEW OF CURRENT LITERATURE

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ANATOMY AND PHYSIOLOGY

340. **Granular Endometrial Stroma Cells.**

By H. HAMPERL. *Obstet. Gynec.*, **11**, 379–387. Apr. 1958. 13 figs. 24 refs.

From the Institute of Pathology of the University of Bonn, Germany, the authors report on certain cells in the endometrium which contain non-metachromatic granules which occur during the secretory phase and in the decidua up until 3-months gestation. These are called "granular endometrial stroma cells" (Körnchenzellen or K cells). Their granules contain a high molecular protein rich in tyrosine and tryptophane. The cells develop from undifferentiated stromal cells, degenerate with retrogression of the decidual cells, and appear outside the uterus only in ectopic decidua. *J. G. Dumoulin*

341. **Experimental Evidence for the Existence of a Uterine Hormone.**

By B. TENNEY, F. PARKER, JR., and S. L. ROBBINS. *Amer. J. Obstet. Gynec.*, **75**, 656–662. Mar. 1958. 3 figs. 4 refs.

The authors had previously shown (*Amer. J. Obstet. Gynec.*, 1955, **70**, 889) that in the rabbit hysterectomy caused degeneration and disappearance of ovarian follicles and the formation in the ovaries of a mass of vacuolated cells—the interstitial body. An aqueous extract from human uteri injected during 12 weeks into 3-months old hysterectomized rabbits inhibited these changes. It is concluded that the human uterus has an endocrine function. *F. J. Browne*

342. **Studies of the Function of the Early Human Trophoblast. III. A Study of the Protein Structure of Mole Fluid, Chorionic and Amniotic Fluids by Paper Electrophoresis.**

By D. G. MCKAY, M. V. RICHARDSON and A. T. HERTIG. *Amer. J. Obstet. Gynec.*, **75**, 699–707. Apr. 1958. 5 tables. 2 figs. 18 refs.

This is a study of the protein composition and structure of liquor amnii and fluids obtained from chorionic tissue and vesicles of hydatidiform moles. The similarity of their protein structure to that of maternal serum suggests that their proteins are derived from the maternal serum by transfer across the trophoblast. *F. J. Browne*

PREGNANCY

343. **Experiences Using the Image-Intensifier for Gynaecological and Obstetric Radiology.** (Erfahrungen bei der Anwendung des Röntgenbildverstärkers in der Gynäkologie und Geburtshilfe.)

By H. BURGER. *Geburtsh. u. Frauenheilk.*, **18**, 937–942. July 1958. 2 figs. 10 refs.

The author has been using an X-ray image-intensifier for 2 years in the department of gynaecology of the University of Munich. The instrument used was that

manufactured by C. H. F. Müller of Hamburg. The principle of the instrument is that X-rays after passing through the subject impinge on a spherical fluorescent screen, whose rays then activate a photo-cathode to release electrons. The electrons are concentrated and collected in a second tube where they are made to produce a fluorescent image which is nine times smaller than the original but one thousand times brighter. This image is viewed through a microscope which converts it to its original size. The maximum field which can be covered by the instrument has a diameter of 12·5 cm. This is adequate for hysterosalpingography and most other procedures. The instrument is mobile. The viewing objective can quickly be replaced by an automatic miniature camera which takes 2–3 pictures per second of 16–22 mm. diameter. Normal X-ray pictures can be taken if required by pushing the apparatus to one side.

The author found the technique adequate and in fact superior to the current radiological methods used for hysterosalpingography. He found that in 65 cases an accurate diagnosis could be made after 30 seconds viewing through the image-intensifier with an exposure of 70kV and 1·5mA. By direct measurement with ionization chambers in the vagina and rectum he calculated that under these circumstances the dose of X-rays to the ovaries was 0·2 r per minute. At the most only 2 pictures were taken of each patient and, if no abnormality was discovered on direct viewing, no pictures were taken. X-ray pictures required an exposure of 64kV and 50mA for 0·08 seconds, giving an irradiation dose to the ovaries of 0·005 r. The maximum dose of irradiation to the ovaries using the image-intensifier for a hysterosalpingogram (including 30 seconds viewing and 2 pictures) is 0·11 r.

The author states that the advantages of the image-intensifier are:

(1) Because of the thousand-fold increase in light intensity of the image the examination can be carried out in a normally lit room and dark adaptation of the observer is unnecessary.

(2) Increased clarity of the image improves the accuracy of diagnosis.

(3) The patient receives only 1/6 of the usual dose of irradiation to the gonads during hysterosalpingography. Technicians and radiologists are likewise exposed to less irradiation.

The intensifier has not proved so successful for obstetric radiology.

Peter J. Huntingford

344. Fetal Electrocardiography Utilizing Abdominal and Intrauterine Leads.

By S. KAPLAN and S. TOYAMA. *Obstet. Gynec.*, **11**, 391–397. Apr. 1958. 1 table. 8 figs. 11 refs.

To date, foetal electrocardiography has been attempted by many with only a little success, and it is still very much in the experimental stage. This study presents results obtained by using abdominal leads and high amplification, and comparing them with those obtained from a single abdominal and a single intra-uterine lead. The intra-uterine lead was introduced through a Drew-Smythe catheter, and its use has demonstrated its superiority over other methods in the quality of tracing obtained.

J. G. Dumoulin

345. Bucladin in the Management of Nausea and Vomiting of Pregnancy.

By J. I. WARGIN. *West. J. Surg. Obstet. Gynec.*, **66**, 235–239. July–Aug. 1958. 43 refs.

After extensively reviewing the literature on nausea and vomiting in pregnancy, the author reports his success with "Bucladin": buclizine hydrochloride 50 mg., pyridoxine hydrochloride 10 mg., scopolamine 0·2 mg., atropine sulphate 0·05 mg., hyoscyamine sulphate 0·05 mg.

A series of 88 patients were treated with an average dose of 1 tablet t.d.s. and 82 produced an "excellent" response although 25 complained of dryness of the mouth and 8 were drowsy. Although there is a large functional element in the aetiology of the condition, the author is very satisfied with the effect of the preparation.

D. C. A. Bevis

346. Foetal Salvage in Early Severe Toxaemias of Pregnancy.

By G. MAIZELS. *S. Afr. med. J.*, **32**, 485–487. May 10, 1958. 7 tables. 3 refs.

The author reports on a series of 37 patients with severe pre-eclampsia admitted to hospital between the 20th and 32nd weeks of pregnancy. In all cases the blood pressure was or subsequently rose above 160 mm. Hg. Eleven patients had a systolic pressure above 200 mm. In 18 cases there was hypertension, albuminuria and oedema, in 10 hypertension and albuminuria, in 1 hypertension and oedema and in 8 hypertension only above 160/100 mm. Nineteen patients did not respond to treatment and after an average of 4·4 days pregnancy was terminated with 1 infant survivor. The 18 patients who responded to treatment spent an average of 46·9 days in hospital before delivery and there were 9 infant survivors. The first 10 days after admission was the critical period, and patients who continued beyond that stage had a 50 per cent chance of a successful pregnancy. Although no patients with a blood pressure above 200 mm. had a live infant, the author states that in a few later cases effective hypotensive therapy produced satisfactory results. No patient with gross albuminuria gave birth to a live child. It is felt that cases for conservative therapy should be selected. Those to be excluded are cases of eclampsia, severe chronic nephritis, severe albuminuria, and persistent chronic hypertension with a systolic blood pressure above 200 mm. in spite of hypotensive therapy.

L. J. Abramowitz

347. Blood Groups, the Rhesus Factor and Toxaemia of Pregnancy. (Blutgruppen, Rh-Faktor und Schwangerschaftstoxikose.)

By H. KYANK and B. KULISCH. *Geburtsh. u. Frauenheilk.*, **18**, 946–950. July 1958. 2 tables. 16 refs.

The authors have reviewed the literature and current theories on this subject. They have analyzed a series of cases from the gynaecological department of the University of Leipzig. From 1950–1955 there were 846 cases of pregnancy toxaemia (including 55 cases of eclampsia) and 1,831 women were delivered who showed no signs of toxaemia. There was no statistical difference between the frequency of the ABO groups or the percentages of Rh-negative mothers in either group.

The incidence of toxaemia in mothers with definite evidence of Rhesus incompatibility was 11·8 per cent (8 of a total of 68 patients) this compares with the overall incidence of toxaemia of 3–5 per cent. All the patients in this group were multiparous. One case of toxaemia was associated with an hydropic foetus and placenta. No evidence of toxaemia was found in 4 other cases of hydrops foetalis.

It is concluded that placental damage is responsible for the increased frequency of toxaemia of pregnancy in multiparae with Rhesus incompatibility.

[The authors do not state their criteria for the diagnosis of toxaemia, nor are any details given of the cases of Rhesus incompatibility. The paper lends support to the arguments recently propounded by J. S. Scott in the Blair-Bell Memorial lecture for 1958.]

Peter J. Huntingford

348. **A Method of Influencing Rh-Sensitisation by Active Immunisation with Anti-D Antibody.** (Die Beeinflussung der Rh-Sensibilisierung durch aktive Immunisation mit animalischem Anti-D-Körper.)

By J. PERKEDI and T. TAX. *Zbl. Gynäk.*, **80**, 1067–1068. July 5, 1958.

By inoculating rabbits with human anti-D antibody, the authors were able to obtain an anti-anti-D serum which is capable of reducing the titre of anti-D antibodies in rabbits immunized with washed and dried human erythrocyte stroma containing the D antigen.

Bruce Eton

349. **Premature Separation of the Normally Implanted Placenta.**

By P. A. NILSEN. *Acta obstet. gynec. scand.*, **37**, 195–260. 1958. 30 figs. 205 refs.

This paper, from the Obstetric Department of Oslo University, is a detailed study of premature separation of the normally implanted placenta (P.S.P.) based on a review of the literature and of 357 cases observed during the last 25 years.

The incidence of P.S.P. was 0·64 per cent, and the maternal and foetal mortality were 2·5 and 65 per cent respectively. The maternal deaths were due to eclampsia (2 cases), necrosis of the liver (1 case), haemorrhage (3 cases), renal damage with anuria (2 cases), and to unknown factors in 1 case. There was no difference in the incidence between primigravidae and multiparae. The duration of labour was less than 12 hours in three-quarters of the cases. About two-thirds of the cases were of a more or less severe nature. No relationship could be determined between P.S.P. and the severity of toxaemia which co-existed in over half of the cases under review. Twenty patients lost more than 2 litres of blood, and in 7 of these coagulation failure accounted for the heavy bleeding. The author describes a method of rapid determination of the fibrinogen level. The fate of fibrinogen is discussed; up to 11·4 g. were found in retro-placental clots, that is an amount approximating that present in the circulating blood.

Energetic treatment of P.S.P. is advocated. "Rapid delivery and prophylaxis against shock are essential." Blood-grouping and fibrinogen analysis should be carried out immediately after admission to hospital. If the foetus is viable and early delivery is unlikely Caesarean section should be done in severe cases. Early artificial rupture of the membranes is recommended. Ample and early blood-transfusion restores the circulation, counteracts tissue hypoxia, relieves fibrinogen deficiency in all but the most severe cases, replaces "other coagulation factors" which may be reduced, and replaces plasma proteins. Only in cases of severe bleeding due to afibrinogenaemia will infusion of fibrinogen be required.

N. Alders

350. **Rupture of the Marginal Sinus of the Placenta: "Abscission Windows."**

By C. L. SCHNEIDER. *Obstet. Gynec.*, **11**, 715–721. June 1958. 4 figs. 16 refs.

Windows opening through the basal, or decidual, plate of the marginal sinus of normal, delivered placentas were studied by the author and called "abscission windows". These windows appear to be lumens of different segments of the venous channels which, during pregnancy, connected the marginal sinus with the underlying marginal venous plexus of the uterus.

Premature rupture of the marginal sinus in this way could permit significant vaginal bleeding, and rupture of the sinus by opening of abscission windows may be the commonest cause of bleeding from the marginal sinus.

Premature rupture of the sinus differs from abruptio placentae in that the latter involves retroplacental separation and arterial haemorrhage. The bleeding from sinus rupture is venous, but diagnosis can only be made by exclusion of abruptio placentae and placenta praevia.

J. G. Dumoulin

351. **The Spontaneous Rupture of Parauterine Veins in the Eighth Month of Pregnancy.** (Über die Spontanruptur parauteriner Venen der linken Uterushinterwand bei einer Gravidität mens VIII.)

By E. PITTROFF. *Geburtsh. u. Frauenheilk.*, **18**, 1059–1062. Aug. 1958. 9 refs.

A case is reported of spontaneous intra-peritoneal rupture of varices of the left uterine veins. A para-1 was admitted at 36 weeks complaining of abdominal pain. She was in a state of mild surgical shock, which gradually increased during the next 24 hours. The uterus was soft and foetal parts were easily felt. The foetal heart remained audible. There was generalized

lower abdominal tenderness. A laparotomy was performed. Just above the left side of cervix 2 bleeding varices were found; these were ligated. A living child was delivered by lower segment Caesarean section. The patient made an uninterrupted recovery.

The aetiology and difficulties of diagnosis of this condition are discussed. The mortality rate in the reported cases is 46 per cent, but this rises to 75 per cent if the varices rupture during labour. The author emphasizes the need for urgent laparotomy in such cases, but this can only be done if the possibility of such an event is kept in mind.

Peter J. Huntingford

352. **Potassium Permanganate Burns of the Vagina. Another Cause of Third Trimester Bleeding.**

By J. C. Caillouette and C. B. Chambers. *West. J. Surg. Obstet. Gynec.*, **66**, 225–227. July–Aug. 1958. 13 refs.

Potassium permanganate in contact with the vaginal mucosa evolves nascent oxygen and produces superficial necrosis; in this reaction potassium hydroxide is formed and acts on the shallow burns to cause penetrating ulcers with resultant bleeding. These ulcers are covered with a brown-black jelly (manganese dioxide) and the appearance is diagnostic. The permanganate absorbed through the ulcers produces intravascular haemolysis and results in lower nephron nephrosis and its ensuing complications. Treatment depends on the condition of the patient; if active bleeding is not present simple irrigation is sufficient, but bleeding may necessitate suture or packing of the vagina, oxycel may be useful here. The serum potassium, icteric index, fluid balance and electrolyte balance must be followed closely for at least 48 hours. Three illustrative cases are described, all were in the third trimester of pregnancy and all responded to treatment. Potassium permanganate should not be prescribed for douches as it is difficult to obtain a true solution and particles may cause these burns.

D. C. A. Bevis

353. **Surgical Closure of the Incompetent Cervix During Pregnancy.**

By R. H. Barter, J. A. Dusbabek, H. L. Riva and J. Parks. *Amer. J. Obstet. Gynec.*, **75**, 511–524. Mar. 1958. 4 figs. 17 refs.

Careful evaluation of the history of a patient who has had repeated abortions is the best method of determining whether the cervix may be incompetent. Sudden loss of liquor amnii at between 16 and 28 weeks is the most striking feature. It rarely occurs in a first pregnancy. Usually there has been a deep tear of the cervix during labour, or during dilatation and curettage after abortion, or it may result from amputation of the cervix. Examination at weekly intervals during pregnancy will reveal effacement and dilatation between the 14th and 26th weeks. This may occur slowly over several weeks or within 1 week. The membranes will be seen bulging at the external os or they may have hour-glassed through the partly dilated cervix. They are not under tension and the uterus is not irritable.

Before the current pregnancy the 22 patients in the authors' series had had a total of 91 pregnancies with 10 surviving infants. The time of operation varied from the 10th to the 27th week of pregnancy, the average being 18 weeks. In the 14 successful cases the average duration of pregnancy was 36½ weeks. The best time for the operation is between the 14th and 18th weeks. After the 20th week excessive effacement of the cervix may make the procedure difficult. A pair of special aneurysm needles, left and right, are used to introduce a purse-string suture after pushing up the bladder. The patient is kept in bed for 10 days after operation and on progesterone for several weeks.

The authors emphasize that the procedure is not a panacea for all abortions. If done indiscriminately the only result is anatomical and psychological trauma without any improvement in the patient's ability to deliver a viable infant.

The article is beautifully illustrated, including operative details.

F. J. Browne

354. **Weight Control During Pregnancy. A New Anorexiant, Phenmetrazine Hydrochloride.**

By C. H. Birnberg and M. E. Abitbol. *Obstet. Gynec.*, **11**, 463–467. Apr. 1958. 2 tables. 3 figs. 19 refs.

Fifty pregnant patients were treated for being overweight during pregnancy with 25 mg. of phenmetrazine hydrochloride (Preludin) three times a day, 1 hour before each meal. No indication was given to the patient as to the purpose of the medication or as to what effect it might produce. No dietary instructions were given.

The mean weekly weight gain of the treated patients was 0·18 pounds compared with 0·94 pounds in an untreated control group. No evidence of toxicity or allergy to the drug was found. Thus, Preludin appears to be a very useful drug in suppressing excessive eating in pregnancy.

J. G. Dumoulin

355. **The Nephrotic Syndrome in Pregnancy: A Review of 20 Cases.**

By L. J. Schewitz and H. C. Seftel. *Med. Proc., Johannesburg*, **4**, 304–305. May 17, 1958. 2 refs.

This condition has received scant attention in obstetrical literature. In all cases except one, diagnosis was made before the 28th week. All patients presented with massive oedema of the lower limbs and blood pressures of less than 120/80 mm. Hg. Urinary investigation revealed normal concentrating power (1,020 or more), proteinuria (Esbach 0·5–24 g./l.) and mixed urinary casts. Serum albumin ranged between 0·6 and 1·7 per cent, and globulin between 1·6 and 4·8 per cent. Plasma cholesterol ranged between 180 and 540 mg. per 100 ml. The diagnosis, particularly in early pregnancy is easily made. In 9 cases there were transient elevations in blood pressure. In only 3 cases did it rise above 150/90 mm. Hg. There were 22 infants born alive from 21 pregnancies. The incidence of prematurity was increased. Although oedema began to subside immediately after delivery, there was no associated improvement

in the biochemical findings or the proteinuria. Follow-up studies have been over short periods, due chiefly to the shifting character of the population served by the hospital. Two complications were a high incidence of sepsis and venous thrombosis. Dextran has been useful in cases with extensive oedema. In no case was therapeutic abortion performed, nor was it necessary to induce labour prematurely. Prophylactic antibiotics and anticoagulants are recommended.

L. J. Abramowitz

356. **Kidney Biopsies in Multiparous Patients with Vascular Renal Disease in Pregnancy.**

By W. J. Dieckmann, C. P. McCartney and J. P. Harrod, Jr. *Amer. J. Obstet. Gynec.*, **75**, 634–655. Mar. 1958. 8 tables. 9 figs. 7 refs.

In 1952 Dieckmann and his colleagues (*Amer. J. Obstet. Gynec.*, **64**, 850) stated that patients who developed permanent hypertension or renal damage following toxaemia of pregnancy had latent or manifest vascular renal disease before pregnancy, and that the pregnancy had exacerbated but not initiated their disease. In the present study renal biopsies were got during pregnancy from the multiparae who currently had toxaemia of pregnancy, or who had had this complication in a preceding pregnancy. They included patients with previous pre-eclampsia or eclampsia, hypertensive disease of pregnancy, chronic glomerulonephritis in pregnancy and chronic pyelonephritis, as well as 10 multiparae whose pregnancies had been uncomplicated by toxaemia.

It was often found to be impossible to diagnose between the advanced lesions of chronic glomerulonephritis, nephrosclerosis and chronic pyelonephritis, so that in 10 per cent of the biopsies the diagnosis was uncertain. In 24 of the 42 patients in whom a clinical diagnosis of chronic hypertension was made renal lesions were absent. This was to be expected as nephrosclerosis is usually a late manifestation of essential hypertension. A significantly large number of patients with histological renal disease get increase of blood pressure and albuminuria between 26 and 34 weeks. The authors feel that this is a result of an exacerbation of the renal vascular disease rather than a superimposed pre-eclampsia. Occult chronic pyelonephritis was found in 4 patients. This, in absence of biopsy, would probably have been diagnosed as chronic hypertension due to chronic renal vascular disease. Normal renal biopsies were obtained in the 9 multiparae whose first pregnancy had been complicated by pre-eclampsia-eclampsia. This supports the contention that pre-eclampsia and eclampsia do not cause permanent renal damage. No renal abnormalities were found in the 10 multiparae whose pregnancies had been uncomplicated by toxaemia.

F. J. Browne

357. **Hydramnios.**

By A. P. Barry. *Obstet. Gynec.*, **11**, 667–675. June 1958. 7 tables. 17 refs.

Out of 13,194 deliveries in the National Maternity Hospital, Dublin, there were 213 cases of hydramnios, 18 of them twin cases. Of the total of 231 infants, 93 were stillborn and 67 died in the neonatal period. Thus the foetal loss was 69 per cent, 58 per cent of which was unavoidable and due chiefly to foetal abnormalities (anencephalus accounted for 88 cases and spina bifida 21).

Acute hydramnios occurred in 7 cases and all the foetuses were lost. The author believes that it might be possible to save some such cases by abdominal paracentesis and continuous drainage of the amniotic sac using a Gibbons catheter or polythene tube.

Chronic cases in which medical treatment alone is unsuccessful should also be treated by paracentesis, remembering that hydrocephalus must be constantly suspected (the commonest cause of ruptured uterus in Ireland). As large amount of fluid as can be obtained should be removed at the time of the tap, being allowed to drip out slowly over several hours. If rapid evacuation occurs, severe accidental haemorrhage may result. It is absurd to imagine that an ordinary high puncture of the membranes with a Drew Smythe catheter will allow a slow release of amniotic fluid. In some cases in which paracentesis has been done it may be necessary to repeat it at a later date if the symptoms have recurred.

J. G. Dumoulin

358. **Normal Pregnancy Occurring in a Cretin. Report of a Case.**

By R. E. Visintine. *Amer. J. Obstet. Gynec.*, **75**, 821–824. Apr. 1958. 7 refs.

This is said to be the fifth reported case of pregnancy in a cretin. Up to the age of 4 years she had not walked or talked but since then had taken 100 mg. desiccated thyroid daily. Thereafter development occurred; she began to walk and talk and at the age of 9 went to school, and by the age of 18 had some ability to read and write. Menstruation began at 15 years and at 22 years she became pregnant. Except for some morning sickness her prenatal course was normal. She continued desiccated thyroid, 60–100 mg. daily, till term when she had a normal spontaneous delivery of a seemingly normal male infant.

F. J. Browne

359. **Toxoplasmosis from the Point of View of the Obstetrician.** (Die Toxoplasmose vom Standpunkt des Geburtshelfers aus.)

By H. Dietel. *Zbl. Gynäk.*, **80**, 910–915. June 7, 1958. 6 refs.

The author considers that a number of stillbirths and neonatal deaths of "unknown origin" are due to congenital infection with toxoplasma. Amongst his last 10,000 births in the city population he encountered 2 cases of toxoplasmosis. Women who have given birth to an affected child may have shown no clinical signs or symptoms during pregnancy. The likelihood of subsequent children being infected is very small. The most common pathological changes in the infected children are hydrocephalus, intra-cerebral calcification and chorioretinitis.

He discusses the difficult problem of prenatal diagnosis. The only diagnostic methods available during the antenatal period are the Sabin-Feldman dye test and a complement fixation test. These prove that the patient may have or may have had an infection, but they do not indicate whether the foetus is affected.

In order to assess the incidence of toxoplasmosis, the author tested 1,021 expectant women during the last weeks of pregnancy. In 32 per cent antibodies were demonstrated. For comparison the tests were also carried out on 1,000 recruits for the police force, where the incidence was found to be 27 per cent.

Amongst 584 women with negative tests, a study of their previous pregnancies revealed abnormalities which could be attributed to toxoplasmosis in 25 per cent. Amongst 260 pregnant women with positive reactions, the corresponding figure was 32 per cent. It is concluded that a single positive serological test for toxoplasmosis provides no evidence for an infection of the foetus.

The author concludes that, with the methods available at present, the chances of prenatal assessment of the risks to the foetus due to toxoplasmosis are poor.

Bruce Eton

LABOUR

360. **Effective Uterine Blood Flow During Labor.**
By H. Payling Wright, N. Morris, S. B. Osborn and A. Hart. *Amer. J. Obstet. Gynec.*, **75**, 3–10. Jan. 1958. 2 tables. 1 fig. 19 refs.

Effective uterine blood flow was measured by finding the clearance time of radioactive sodium injected into the uterine muscle in 46 normal women, 20 of whom were in the early first stage of labour, and 26 in the late first stage. In the early first stage all but 3 showed normal clearance; of these 3, 2 had frequent strong contractions, but the third seemed normal. In the late first stage 14 had prolonged clearance. In most of these there were abnormalities such as very frequent contractions, long labour ending in forceps delivery, or long rupture of membranes, and in 3 of them there was long labour and foetal distress. The authors consider that while in normal labour, though some diminution of blood flow must occur when contractions are frequent, there is usually sufficient flow to ensure proper oxygenation of the foetus. If however, oxygenation is already poor as in prolonged pregnancy or pre-eclampsia, even the transient diminution of blood flow during contractions might endanger the foetus. In the present series the 3 longest clearance times, i.e., 13·5, 17·0 and 18·5 minutes (upper limit of normal, 6 minutes) were associated with foetal distress.

[This paper helps to explain the occurrence of foetal distress in the first stage of labour even though the membranes are intact. It would have been helpful if the tables had shown whether at the time of injection the membranes were intact, or if ruptured, how long they had been so, for escape of liquor allows uterine retraction, and thus must of itself diminish utero-placental blood flow.]

F. J. Browne

361. **Castor Oil as an Adjunct to Induction of Labor: Critical Re-evaluation.**
By G. C. Nabors. *Amer. J. Obstet. Gynec.*, **75**, 36–38. Jan. 1958. 2 tables. 14 refs.

In a consecutive series of 114 inductions of labour 4 methods were used, namely (1) rupture of membranes plus subcutaneous pitocin; (2) the same with enema; (3) the same plus castor oil instead of enema; (4) the same plus castor oil and enema. It was concluded that castor oil was without value in starting labour.

F. J. Browne

362. **Dangers Attending Elective Induction of Labour.**
By E. H. Bishop. *J. Amer. med. Ass.*, **166**, 1953–1956. Apr. 19, 1958. 3 refs.

The purpose of elective induction of labour is to make the practice of obstetrics easier, and if it can be performed without increasing the hazards to either the mother or the baby it may then gain the same acceptance as other artificial procedures in normal labour, such as "prophylactic forceps", episiotomy, and analgesia.

The author studied the course of induced labour in 325 patients in comparison with the course of spontaneous labour in 1,290 patients. All were healthy multiparas at the Pennsylvania Hospital. The spontaneous delivery rate in the highly selected induction group was 50·8 per cent and in the control group 24·4 per cent. There was no appreciable increase in maternal or foetal complications.

The obstetrician who contemplates elective induction of labour must be aware of all the dangers that are inherent in induction, and for this reason certain rigid rules were followed in the selection of patients for induction. Good facilities and personnel with adequate experience are essential. The patient should be prepared emotionally and physically, and she should be a multipara at or near term with the vertex presenting without any disproportion. The cervix should be 60 per cent effaced and at least 3 to 4 cm. dilated. After rupture of the membranes oxytocin is given by intravenous drip (1 unit in 100 ml. at 25 drops per minute).

This group of cases of induced labour represented about 20 per cent of the total cases, and this is about the maximum number of inductions that should be done in any group of patients. If this percentage is exceeded, a slight but definite increase in the number of complications must be anticipated.

[The dangers are well stated and the criteria so strict that the onset of labour would appear to be inevitable. Nevertheless it is doubtful whether the procedure will meet with general approval.]

D. W. James

363. **Comparison of Oxytocic and Vasopressive Properties of Syntocinon (Sandoz), Orasthin (Hoechst) and Oxystin (A.W.D.).** (Vergleichende Untersuchungen über die uterus-wirksamen und blutdrucksteigernden Eigenschaften von Syntocinon (Sandoz), Orasthin (Hoechst) and Oxystin (A.W.D.).)
By H. Siener. *Zbl. Gynäk.*, **80**, 903–910. June 7, 1958. 3 figs. 2 tables. 28 refs.

Syntocinon is a synthetic oxytocin having all the pharmacological and clinical actions of the natural hormone.

The author set himself the task of comparing the actions of synthetic oxytocin with those of purified commercial oxytocic preparations extracted from animal pituitary glands ("Orasthin", "Oxystin"). The presence of traces of vasopressin (on the average 5 per cent) has always been considered a drawback of the natural extract.

In a series of 35 patients records of the blood pressure and of uterine contractions (using external tocography) were obtained following slow intravenous injection of 3 units of one of the three drugs. The experiments were carried out half to five hours post-partum. It was found that the oxytocic action of the three preparations was identical. All three drugs produced a slight rise in blood pressure, but there was no significant difference between their vasopressive effects.

The advantage of synthetic oxytocin over the natural products is that its vasopressive action is more likely to be constant. It would seem that there is thus no physiological difference between these preparations and that the oxytocin molecule has normally a certain vasopressive action.

Bruce Eton

364. **Rupture of the Uterus: Report on a Further Series of Cases which Occurred in Bantu Parturients of Johannesburg during 1956–1957.**

By D. W. P. LAVERY. *Med. Proc. Johannesburg*, **4**, 299–305. May 17, 1958. 2 tables. 1 ref.

The author reports on 49 cases of uterine rupture which he compares with a series of 50 cases published in 1955. Forty cases were not booked. In 24 patients rupture followed previous Caesarean section or myomectomy. Two sections had been classical. In only 2 of the 24 cases was rupture easily diagnosed. Manual exploration of the uterus has become a routine procedure after delivery following previous Caesarean section. In only 2 cases was rupture complete. Nineteen infants were born alive and 5 were stillborn. No mothers died in this group.

There were 13 patients in whom obstetrical interference *per vaginam* contributed to uterine rupture, including cases of internal version, craniotomy, and forceps delivery for posterior positions. There were 2 maternal deaths. Rupture was complete in 5 and partial in 8 cases. Hysterectomy was performed in 2 patients and repair in 5. Conservative treatment was chosen in 6 patients, many of whom refused operation.

In 15 cases spontaneous primary rupture occurred. Thirteen were cases of neglected labour. Rupture was complete in 13 and incomplete in 2 cases. Eleven infants were stillborn, 3 were born alive and 1 was not delivered.

There were 9 maternal deaths in 49 cases. Where possible attempts were made to repair the uterus. Of the 49 cases, 17 were sterilized.

L. J. Abramowitz

365. **Oxygen Therapy for Foetal Intra-Natal Hypoxia, Alternating with Inhalation Analgesia.** (Die Sauerstofftherapie der fetalen Hypoxie in der Geburt im Wechsel mit der Anwendung eines Geburtsanalgetikum.)

By A. GÖBEL. *Zbl. Gynäk.*, **80**, 861–868. May 31, 1958. 2 figs. 1 table. 43 refs.

The perinatal mortality up to the fourth day of life amounts to 50 per cent of the infant mortality during the first year of life. In most cases of post-partum asphyxia, a condition of hypoxia or anoxia begins before birth. Therapeutic measures for preserving the child's life should not be delayed until after the delivery of an asphyxiated child but the aim should be to relieve the oxygen lack *in utero*.

An apparatus is described for inhalation of a trilene and air mixture for analgesia during uterine contractions, and a 50 per cent oxygen and air mixture during the intervals. This is suggested for use in all cases where there is evidence of foetal hypoxia, irrespective of its cause.

Bruce Eton

366. **Scalp Traction in Obstetric Practice.** (Die Galeazange in der geburtshilflichen Praxis.)

By K. VARGA and L. VÁCZY. *Geburtsh. u. Frauenheilk.*, **18**, 1048–1059. Aug. 1958. 6 tables. 1 fig. 11 refs.

From the University of Budapest comes a paper reporting the results of 179 deliveries, from 1937 to 1953, in which scalp traction was used. Willett's forceps were applied in 1·1 per cent of cases in 1937, but by 1953 this figure had fallen to 0·1 per cent, mainly because of the increased use of Caesarean section. The indications for scalp traction were placenta praevia, prolapse of an arm or the umbilical cord, eclampsia and uterine inertia (132 cases). In 85 per cent scalp traction achieved the desired end-result.

In 16 cases the foetus was already dead before the forceps were applied. In the remainder the foetal mortality was 16·5 per cent. In 50 per cent of the surviving babies complications of the scalp wound were encountered, the severity of these being directly related to the duration of traction and the position of the foetal head in the pelvis when the forceps were applied. Fifty-five of these children were seen from 6–16 years after delivery; 31 of them had scars of the scalp which were bald, and 6 of them were mentally deficient and either spastic or epileptic. The incidence of puerperal pyrexia was 26·5 per cent.

The use of scalp traction is recommended with minor degrees of placenta praevia in which rupture of the membranes does not control bleeding, after reposition of a prolapsed arm or umbilical cord, in eclampsia and uterine inertia in order to hasten the course of labour and with a dead foetus.

[This paper is of interest as it describes a large series of cases of an obstetric procedure which is seldom performed in this country today. The results hardly justify the authors' final list of indications for the application of Willett's scalp forceps.]

Peter J. Huntingford

367. **Shoulder Dystocia.**

By B. C. SCHWARTZ and D. M. DIXON. *Obstet. Gynec.*, **11**, 468–471. Apr. 1958. 6 refs.

Shoulder dystocia occurs approximately once in each 500 deliveries. It is closely associated with maternal obesity, excessive-sized foetuses, excessive weight gain, and a history of large siblings. The two main methods of overcoming shoulder dystocia at delivery are traction on the head combined with fundal pressure, and extraction of the posterior arm and shoulder. This latter is the better method in difficult cases, even though the humerus may sometimes be fractured.

The hand is inserted into the maternal pelvis along the curvature of the sacrum. The humerus is found and followed to the ante-cubital fossa: pressure is made in this area. As the arm flexes, the forearm is grabbed and swept across chest and face of the foetus, and out of the vagina. Cleidotomy should be reserved for the dead foetus.

J. G. Dumoulin

368. **Ergometrine with Hyaluronidase: Speed of Action.**

By M. P. EMBREY and W. J. GARRETT. *Brit. med. J.*, **2**, 138–139. July 19, 1958. 2 figs. 10 refs.

Records of uterine contractility were obtained from 30 patients early in the puerperium using the "Oxford" tocograph in some cases and the intra-uterine balloon method in others. Exact measurements were made of the delay between injection and response of (*a*) intravenous ergometrine, (*b*) intramuscular ergometrine, and (*c*) intramuscular hyaluronidase-ergometrine mixture (0·5 mg. ergometrine in each case). The average latent periods in these groups were (*a*) 41 seconds, (*b*) 7 minutes, (*c*) 4 minutes 47 seconds.

The authors observe that, in the treatment of emergency haemorrhage, intramuscular ergometrine with hyaluronidase cannot compete with ergometrine given intravenously. They found that the ergometrine-hyaluronidase mixture gave more uniformity of action than intramuscular ergometrine alone, but they question whether the relatively slight increase in speed of action of the former warrants its adoption routinely in the second stage of labour. They also point out that the addition of hyaluronidase to the injection quadruples the cost.

R. W. Grayburn

369. **New Method for Speeding Up Placental Blood Transfusion.** (Neue Methode zur schnelleren Plazentalbluttransfusion.)

By E. SALING. *Zbl. Gynäk.*, **80**, 977–982. June 21, 1958. 2 figs. 11 refs.

The majority of authors consider that it is to the advantage of the child to recover much of the placental blood before the cord is divided after delivery and Saling lists the various reasons in favour of delayed division of the cord. The drawback of this practice, however, is that cord pulsation ceases only after three to five minutes. During that time it becomes more difficult to attend adequately to the immediate requirements of both mother and child.

As a compromise the author suggests a method of speeding up placental transfusion so that it is completed within two minutes at the latest. He advises that the two umbilical arteries should be compressed with two blunt clamps. Blood can therefore not leave the child while the umbilical vein drains placental blood. The child should be kept below the level of the uterus during that time by placing it between the mother's legs, while its air passages are being cleared. The mother's sacrum is raised on a bolster.

By measuring the amount of blood obtainable from the placental end of the cut umbilical vein after various time intervals experimental evidence was obtained that 90 per cent of the placental blood passes over to the child within 1½ to 2 minutes.

In 110 children in whom ligation of the cord was delayed the average haemoglobin value on the next day was 123·1 per cent and the red cell count 5·88 million. These figures are contrasted with those of 169 children where the cord was ligated about 1½ minutes after birth without previous clamping of the arteries: the average haemoglobin level was 114·0 per cent and the red cell count 5·44 million.

The main value of the placental transfusion is, however, the building up of a better store of iron in the reticulo-endothelial system of the liver and spleen, particularly in premature children, twins and children who are going to be fed artificially and are therefore more prone to develop iron deficiency anaemia.

Bruce Eton

ANAESTHESIA

370. **Experiences with Steroid Anaesthesia in Gynaecology and Obstetrics.** (Erfahrungen mit der Steroidnarkose in der Gynäkologie und Geburtshilfe.)

By R. SCHEELE. *Geburtsh. u. Frauenheilk.*, **18**, 942–946. July 1958. 1 table.

An inactive steroid derived from progesterone (sodium hydroxypregnanedione succinate, which is sold as "Viadril" (Pfizer) in the U.S.A. and as "Presuren" (Schering) in Germany), has been used as the anaesthetic for 120 gynaecological and obstetric operations. Barbiturates are contra-indicated as sedatives on the night before operation and as pre-medication when the steroid is to be used, therefore antihistamines were substituted for this purpose. In every case an antihistamine was given 2 hours before operation followed by pethidine and atropine 1 hour later. Anaesthesia was induced by the rapid injection of 1 g. of "Presuren" dissolved in 20 ml. of physiological saline. Deep sleep followed 3–5 minutes after the injection and relaxation was also obtained so that an airway was necessary. No phase of excitation was encountered and no alteration of blood pressure, pulse or respiration rate was noticed. In most cases relaxation was complete enough to enable the patient to be intubated. However, the author recommends the use of relaxants to facilitate this procedure should it be necessary, although only half the

usual dose of such drugs should be used. Adequate anaesthesia lasted for 1–1½ hours.

The drug was used for 120 operations, 24 of the patients being over 60 years of age (it was in the elderly that the author felt the drug was most useful). In 110 of the cases the only anaesthetic used was 1 g. of "Presuren". In 2 cases a further injection of 0·5 g. was necessary to maintain anaesthesia. In 4 cases at the beginning of the series intubation was used, but this has since been found unnecessary. In 4 cases relaxation was inadequate and "Presuren" was supplemented by nitrous oxide and ether. The operations performed were 55 vaginal hysterectomies (including 9 radical operations), 10 abdominal hysterectomies, 19 laparotomies, 7 Caesarean sections, 24 vaginal repairs, 2 vulvectomies and 3 obstetric manipulations.

The only complications were minor ones. There were 5 cases of superficial thrombophlebitis related to the site of injection and it is recommended that small veins of the hand and feet be avoided. Some patients were very restless on recovery, but this was easily controlled with pethidine. The author noticed an increased tendency for capillary oozing especially during vaginal repairs, but there was no increase in the incidence of post-operative haemorrhage. Three babies delivered by Caesarean section under "Presuren" anaesthesia required resuscitation.

Peter J. Huntingford

PUERPERIUM

371. **Post-partum Bowel Function.**

By A. E. Long. *Obstet. Gynec.*, **11**, 415–420. Apr. 1958. 5 tables. 10 refs.

The bowel function of 578 patients was studied post-partum. Constipation in pregnancy may be due partly to decreased smooth muscle tone, and normal tone is not immediately regained post-partum. The patient often has a temporary lack of bulk because of the cleansing enema given before delivery and the fact that she has missed some meals.

Three methods of post-partum bowel management were investigated. One group was given 30 ml. of milk of magnesia daily, one group a soluble vegetable gum to make up bulk, and the third group was given no medication at all. Enemas were given if requested by the patient.

Results obtained by the last two methods were superior to the first, suggesting that normal bowel function will re-establish itself spontaneously if permitted to do so or if stimulated by a non-irritating bulk laxative. Although some cases may still need enemas, the routine use of these is unnecessary.

J. G. Dumoulin

INFANT

372. **Newborn Blood Oxygen. A Method of Increasing the Partial Pressure of Oxygen in the Blood of the Newborn Infant.**

By J. H. McClure. *Obstet. Gynec.*, **11**, 696–703. June 1958. 2 figs. 3 tables. 18 refs.

The purpose of this investigation was to determine if oxygen administered through a face mask to the woman in labour increased the partial pressure of oxygen in the blood of her foetus. Oxygen was given at the rate of 10 litres per minute through a B.L.B. mask when the patient was estimated to be within 1 hour of delivery. All patients were delivered vaginally and received either pudendal block or no anaesthetic. There were 15 such cases and 19 controls; the oxygen treated group had a higher partial pressure of umbilical vein oxygen than the control group. The average partial pressure in the oxygen treated group was 38 mm. Hg compared with 29 mm. Hg in the controls. The author argues that there is probably thereby an increase in the oxygen supply to the foetus of 1 ml. of oxygen per 100 ml. of blood.

J. G. Dumoulin

373. **The Significance of Pulmonary Hyaline Membranes in Newborn Infants.**

By P. Gruenwald. *J. Amer. med. Ass.*, **166**, 621–623. Feb. 8, 1958. 2 figs. 6 refs.

Pathological studies of pulmonary hyaline membranes and speculations about their significance have been unrewarding because these membranes appear as secondary manifestations in lungs affected with a variety of abnormal conditions. Three kinds of conditions are common: (1) atelectasis in premature infants; (2) aspiration of vernix caseosa; and (3) other conditions seen especially in infants born of diabetic mothers or delivered by Caesarean section. Hyaline membranes are not found in infants who have never breathed air, but the reason for this is unknown.

Histological evidence is presented to show that pulmonary oedema and uneven aeration of the lungs precedes the formation of hyaline membranes in premature infants. A few full-term infants surviving only a short time after severe distress show true vernix membranes. Some infants of diabetic mothers are really premature in spite of their overweight, and these cases show the characteristics of atelectasis of premature infants. Others, as well as mature infants delivered by Caesarean section show diffuse pulmonary oedema but only scattered membranes. It is suggested that the investigation of the underlying disease may be more profitable than studying hyaline membranes.

D. W. James

374. **Pulmonary Hyaline Membrane Contamination of the Lungs by Fluid of the Birth Canal. Studies in Rabbits Demonstrating a Hazard of Obstetric Analgesia.**

By F. F. Snyder. *Obstet. Gynec.*, **11**, 599–616. June 1958. 12 figs. 34 refs.

Evidence that foetuses breathe the fluid which surrounds them during labour may be linked to establishment of the origin of pulmonary hyaline membrane disease. To what extent foetal respiration occurs during the second stage of labour may be revealed by the entrance into the lungs of the contents of the birth canal. The author is able to show that there is a striking increase

in contamination of the foetal air passages of the rabbit with fluid and cells of the birth canal following the administration of various analgesic agents during labour.

After labour complicated by foetal and neonatal deaths following meperidine (pethidine), alphaprodine, methadone, or morphia derivatives, the lungs were contaminated with blood, epithelial cells, and debris in 95 per cent of 281 autopsies of stillborn rabbits and newborn that died; large areas of the alveoli and bronchioles of both lungs were involved in 56 per cent, compared with none of 164 newborn controls. The presence of large amounts of this vaginal debris in the foetal lungs is evidence of foetal respiration in the second stage of labour, and it increases in amount with an increase in the duration of labour.

The demonstration of foetal respiration during labour affords a clue to the origin of pulmonary hyaline membrane disease. The entrance of the contents of the birth canal into the foetal air passages during labour accounts for the origin of foreign matter in the lungs of the newborn. With the entrance of air into the air passages this foreign matter is displaced in a membrane-like layer along the walls of the alveoli and bronchioles.

J. G. Dumoulin

GYNAECOLOGY

375. Abnormal Vaginal Discharge. A Preliminary Report on the Work Done by the "Vaginal Discharge Clinic" of the Groote Schuur Hospital, Cape Town,

By F. N. CHARNOCK. *S. Afr. med. J.*, **32**, 556–559. May 31, 1958. 6 tables, 29 refs.

The author discusses the scope of the special clinic with regard to investigations, allaying fears of cancer and syphilis and the detection of early cases of genital carcinoma. The incidence of defaulters was high and husbands were not keen to report for examination. The causes of vaginal discharge were: Trichomonas 49·2 per cent, monilia 24·5 per cent, trichomonas and monilia 4·6 per cent, and non-specific 21·7 per cent. Papanicolaou smears were most useful for the detection of trichomonads.

Treatment of trichomonas infection is continued for 8 weeks with S.V.C. or Floraquin pessaries. Treatment was repeated for a few days following menstruation over the next few months. Infection in the male is discussed, and although few males presented for investigation in this series, the use of a condom was advised for 3 months. Tritheon proved disappointing. In some resistant cases in the female oestrogynedron was tried with success. Mycostatin proved superior to gentian violet in monilial infections.

The non-specific group is discussed, particularly in relation to *Haemophilus vaginalis*. The high incidence of infection in the male is noted. Triple sulfa cream and Hexetidine (Sterisil) seemed to be most effective in the female and Mysteclin in the male.

L. J. Abramowitz

376. Colposcopy—Neglected Method of Cervical Evaluation.

By W. R. LANG. *J. Amer. med. Ass.*, **166**, 893–897. Feb. 22, 1958. 4 figs. 5 refs.

The colposcope is essentially a binocular microscope of low power with an attached light source. Although first described more than 30 years ago it has been almost completely neglected. It has now been improved and provides an additional means of examining surface morphology. Atypical changes are classified as: (1) simple leukoplakia; (2) ground leukoplakia; (3) mosaic leukoplakia; and (4) non-iodine-staining areas. True erosions and abnormal vascular patterns are also noted. The technique is described and includes colour colpophotography.

It is possible to distinguish between squamous and columnar epithelium, and of great interest is the intermingling of the two types, the so-called transformation or regeneration zone. This zone has three manifestations: islands of columnar epithelium in squamous epithelium, gland openings in squamous epithelium, and Nabothian cysts. It is in the transformation zone that atypism and malignancy are said to originate. The colposcopic findings in 49 cases of cervical carcinoma from the Jefferson Medical College and Hospital are summarized.

Colposcopy is a useful clinical method of following the changes in the cervix and also shows the best place to obtain a specimen for biopsy. In addition, it may provide research opportunities in studying morphogenesis of incipient cancer, radiation changes, and recurrence.

D. W. James

377. "Spider Cells", A New Inhabitant of Peritoneal Fluid. A Preliminary Report.

By H. W. HORNE, JR., and C. AUDET. *Obstet. Gynec.*, **11**, 421–423. Apr. 1958. 1 table. 1 fig. 2 refs.

Peritoneal fluid aspirated at the time of laparotomy in some infertile women has revealed the presence of spider-like structures of round contour about two-thirds the size of red blood cells and having about 25 discrete cilia around the circumference. These "spider cells" were found in 3 out of 10 laparotomies. All attempts to culture them have failed to date, so it is not known if they are parasites, and their nature and significance have yet to be determined.

J. G. Dumoulin

INFECTIONS OF THE REPRODUCTIVE ORGANS

378. Acute Salpingitis. Views on Prognosis and Treatment.

By E. HEDBERG and S. O. SPETZ. *Acta obstet. gynec. scand.*, **37**, 131–154. 1958. 3 figs. 25 refs.

A series of 216 cases of acute salpingitis (96 of them gonorrhoeal, and 120 "septic"), which were treated at the Gynaecological Clinic in Gotheburg (Sweden) between 1946 and 1953, are discussed. Gonorrhoeal salpingitis was treated with penicillin (800,000 units daily for at least 5 days), and "septic" salpingitis with simple rest in bed,

with sulpha-drugs, or (in vary acute cases) with penicillin and streptomycin. Of the total series, 181 patients (84 per cent) were followed up for at least 4 years.

It was found that the effect of treatment, and the immediate and remote prognosis, depended on the length of time between onset of the symptoms and commencement of treatment. The total incidence of pregnancy after treatment was 30 per cent. However, if patients over 40 years of age, those that practised contraception, unmarried women, and those who had later both Fallopian tubes removed, were excluded, the incidence of pregnancy was as high as 60 per cent.

Of 30 patients whose gonorrhoeal salpingitis was treated with penicillin, and in whom hysterosalpingography was performed on discharge from hospital, 24 (or 80 per cent) showed patency of one or both Fallopian tubes.

N. Alders

379. **The Problems of Diagnosis in Genital Tuberculosis in Women. New Methods of Bacteriological Diagnosis in Genital Tuberculosis.** (Problema diagnosticilui in tuberculoma genitala la femeie.)

By A. ALDEA, I. FILIPESCU and A. CRISTEA. *Obstet. Ginec.* (*Bucarest*), 143–150. Mar.–Apr. 1958. 13 refs.

The authors describe methods of bacteriological diagnosis of tuberculosis of the genital tract. In 1954 they first described a method of culture using the blood obtained at curettage, which they consider superior to methods using menstrual blood. The blood is obtained by curettage in the pre-menstrual phase, when tuberculous follicles are maximally developed, or from patients with amenorrhoea. The blood and endometrial fragments are cultured in several tubes in Lowenstein-Jensen medium. This method has been used in 41 cases with a clinical diagnosis of tuberculosis. Positive results were obtained from the blood itself in 56 per cent of cases.

They have also cultured cervical mucus. In 24 cases investigated they had 50 per cent of positive results. As cyclical changes occur in the cervical mucus repeated investigations are necessary. They had one interesting case in which biopsy was negative but the test on the cervical secretion was positive.

Sylvia Lerer

380. **The Relative Value of Culture and Endometrial Biopsy in the Diagnosis of Genital Tuberculosis.**

By I. HALBRECHT. *Amer. J. Obstet. Gynec.*, **75**, 899–903. Apr. 1958. 1 table. 2 figs. 11 refs.

Female genital tuberculosis is now, thanks to routine endometrial biopsy in sterility, and the growing use of cultures of menstrual and intermenstrual discharge when tuberculosis is suspected, recognized as occurring oftener than used to be thought. The author has introduced the use of cultures of vaginal and cervical secretion, especially in amenorrhoea of virgins, from whom menstrual discharge cannot be got.

The present report includes 120 cases which were diagnosed either by endometrial biopsy or by culture of uterine discharges or both. When the 2 methods gave contradictory results the biopsy was repeated and the pathogenicity of the acid fast bacilli which grew in the cultures was checked by guinea pig inoculation. The cultures of menstrual discharge were repeated until at least one or two positive or ten negative results were got. In 54 cases biopsy and culture both gave positive results. In 38 the cultures were positive and biopsy negative. In 11 the endometrium showed tuberculous lesions but cultures were negative, and in 17 cases cultures alone were used and were all positive. Of the 103 cases in which both methods were used simultaneously biopsy gave positive results in 65 (63 per cent) whereas the cultures of the uterine discharge helped to detect the disease in 92 (90 per cent.).

While routine biopsy in sterility has helped to uncover many unsuspected cases, without recourse to culture many would remain undiscovered. Moreover by cultures it is possible to demonstrate the tuberculous nature of many inflammatory pelvic masses, while they are the only method available for the diagnosis of the early tubal stage of genital tuberculosis. The author considers that while hysterosalpingography has value in diagnosis of tuberculous tubes, bacteriological confirmation is obligatory. He was in this way, able to confirm the tuberculous nature of tubal occlusion diagnosed by salpingography in 39 out of 40 cases in which radiographic signs of tuberculosis were present, while the endometrial biopsy gave positive results for tuberculosis in only 20 of these cases.

Tuberculous lesions of the endometrium and tube are among the most paucibacillary of all tuberculous foci. This explains why cultures were so rarely positive. In most cases no more than one out of three or four cultures were positive and in a few cases cultures had to be repeated up to 10 times before one positive result was reached. Both biopsy and culture have their advantages and should be used simultaneously whenever possible.

F. J. Browne

381. **Clinical Experiences in 550 Cases of Female Genital Tuberculosis.** (Klinische Erfahrungen in 550 Fällen weiblicher Genitaltuberkulose.)

By F. KOVACS and I. GAVALLER. *Zbl. Gynäk.*, **80**, 1000–1046. June 28, 1958. 1 fig. 5 tables. 148 refs.

The authors review a series of 550 cases of genital tuberculosis in the female. The incidence of female genital tuberculosis is probably higher than is generally thought, because with the general increase in the number of curettages performed between 1927 and 1956, the percentage of genital tuberculosis detected rose during the 30 years from 0·2 to 2·8.

85·2 per cent occurred during the reproductive period, between the ages of 15 and 40. The incidence is particularly high in women between 21 and 25 years of age, probably because infertility following marriage brings these cases to light. Of 464 married women, 74·3 per cent suffered from primary infertility, which is the most common and characteristic symptom of genital tuberculosis, and 7·2 per cent had previous

unsuccessful (including 9 extra-uterine) pregnancies. Even the 85 (18·3 per cent) successful pregnancies had occurred some years, in some instances between 10 and 15 years, before the appearance of the disease. Pregnancy occurring in a woman suffering from the disease constitutes a serious and dangerous complication. Patients known to be suffering from genital tuberculosis should be advised to postpone marriage.

The authors disagree with the general view that in about 40 per cent of cases the endometrium is not affected and curettage could not therefore provide material for diagnosis, because they obtained histological evidence in 77 per cent of cases. They disapprove of strip biopsies and advocate thorough curettage in all cases, if necessary under antibiotic cover. They base their higher incidence of positive curettings on the extended use of diagnostic curettage, which should only be carried out in specialized departments after exclusion of acute or subacute inflammatory processes. Exploration of the uterus may be considered in cases of primary sterility, particularly in patients with a history of pleurisy or peritonitis. In the presence of an adnexal tumour in a virgin, curettage is hardly necessary for diagnostic purposes.

Bacteriological cultures are very useful, particularly when acute or subacute adnexal inflammation contraindicates diagnostic curettage. Animal inoculation offers an advantage over culture because it proves that the acid-fast organism is in fact virulent.

The authors discuss conservative treatment with chemotherapy and antibiotics. To establish evidence of cure is difficult. The authors' criteria were negative findings 3, 6 and 12 months after completion of treatment. In 9 patients they found after subsequent surgical removal that a previously infected endometrium had healed whereas the tubes remained affected. This indicates that negative curettings do not always imply a complete cure. They conclude that bacteriostatic drugs, although very valuable in the treatment of female genital tuberculosis fail to achieve a cure in very many cases (perhaps 85–90 per cent). Much depends on early diagnosis and vigorous treatment. The cure of tubal disease can only be proved by histological examination of the tubes after removal.

The main focus of the disease is often inaccessible to antibiotics as it is encapsulated by fibrosed and caseous tissue. It is in the treatment of such lesions that surgery is most useful.

The following indications for surgery are listed: occurrence of the disease in women over 40 years; in young childless women, if conservative treatment has failed; in young parous women if an adnexal tumour is present; symptoms due to causes which can only be relieved by surgery (extensive adhesions, fixed retroflexion, large adnexal tumour); and if a patient is not in a position to undergo prolonged conservative treatment and follow-up supervision.

[Although the incidence, diagnosis, prognosis and treatment are discussed at great length, the authors fail to produce statistical evidence from their own work in support of some of their views.]

Bruce Eton

382. The Treatment of Tuberculous Salpingitis.

By Åke Rydén. *Acta obstet. gynec. scand.*, **37**, 114–130, 1958. 9 figs. 163 refs.

This is a review of the literature and of 122 personal cases which were treated at the Karolinska Hospital in Stockholm and the Women's Clinic in Karlskrona during the years 1947 to 1957. A number of pertinent questions are posed and answered.

Can tuberculous salpingitis heal spontaneously? This should be possible as patients are occasionally encountered in whom the radiological findings strongly suggest the presence of tuberculous salpingitis, whilst microscopical examination of the specimens obtained at operation and bacteriological examination does not reveal any evidence of active tuberculosis, although areas of calcification on the tubal walls or the ovaries suggest a tuberculous origin of the lesion; tuberculous endometritis may co-exist. However, such cases are too rare to justify waiting for spontaneous cure to occur.

Do all patients with genital tuberculosis require treatment? Even if the disease does not produce symptoms (apart from sterility) there is always some danger of spread of the infection, and all cases should be treated.

Can cure of tuberculous salpingitis be achieved with antibiotics alone? Whilst energetic antibiotic therapy usually results in healing of tuberculous endometritis in one or two months, tuberculous salpingitis (which co-exists in practically all cases of endometritis) requires treatment over a much longer period. Out of 30 cases in the author's series in which the tubes were partially or completely removed at the conclusion of antibiotic treatment of 4 to 6 months' duration microscopy revealed persistence of the tuberculous lesion 17 times. A minimum period of one year of antibiotic treatment is advised.

Should antibiotic treatment alone, surgery alone, or both methods be used? This question cannot be answered fully yet. However, the author suggests that: (*a*) If surgery is the method of choice it should be preceded and followed by antibiotic treatment; the operative mortality of 5 to 25 per cent which obtained before antibiotics were used, has been reduced to negligible figures since the introduction of antibiotic therapy. (*b*) When primary antibiotic therapy proves unsuccessful, surgery is indicated.

What are the patient's chances of conceiving and bearing a child following antibiotic treatment? In no conservatively treated case of the author's series did intra-uterine pregnancy occur. Out of 2,118 treated patients reported in the world literature, 48 (2·2 per cent) conceived and carried the pregnancy to term, 20 had ectopic pregnancies, and 12 aborted intra-uterine pregnancies. In 50 to 70 per cent of cases of tuberculous salpingitis both tubes are occluded, and it is most unlikely that conception can occur in these patients even if the process is cured by antibiotics. Where one or both tubes are patent at the commencement of the treatment, the chances of the patient bearing a viable child are estimated as 5 per cent. However, it is hoped that the discovery of new antibiotics superior to those now in

use, and lengthening of the duration of treatment may increase the chances of successful pregnancies.

Should radical operation be done? The uterus and part or the whole of both ovaries can and should generally be preserved.

What should be done when genital tuberculosis is an accidental finding at laparotomy? If operation on the reproductive organs is technically easy it should be done, and followed by antibiotic therapy. Where operation would obviously be technically difficult the abdomen should be closed, antibiotic treatment should be given, and operation may be carried out 2 to 3 months later.

What antibiotics should be used? Streptomycin and INH have been found best. There is no room for X-rays and intra-uterine radium in modern treatment of genital tuberculosis.

N. Alders

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

383. **Epidermoid Carcinoma of the Vulva. An Analysis of 238 Cases. Part I. Etiology and Diagnosis.**

By T. H. Green, Jr., H. Ulfelder and J. V. Meigs. *Amer. J. Obstet. Gynec.*, **75**, 834–847. Apr. 1958. 11 tables. 10 refs.

In the past 25 years 238 patients with epidermoid cancer of the vulva, not including cases of cancer of the urethra or gland of Bartholin, Bowen's disease, Paget's disease, basal cell cancer or malignant melanoma, were admitted to hospital. The youngest patient was 30 and the oldest 102 years. Diabetes was present in 8·8 per cent but without any diabetic vulvo-vaginitis. Three-fourths of the diabetics had leukoplakia of the vulva. Vulval cancer was relatively frequent in single nulliparous women and there was a tendency to an early menopause, to obesity, hypertension, and premature arteriosclerosis. There was a high incidence of multiple primary malignancies, and 13 per cent had cancer at other sites either before or after the development of the vulvar cancer. One patient had three independent cancers of breast, cervix and vulva and there was a family history of cancer in 21 per cent, which suggests that some carcinogenic factor is at work. Vulval leukoplakia was present in 72 per cent. As a preventive measure therefore simple vulvectomy with removal of as much of the affected skin as possible should be considered in leukoplakia, especially as there is no satisfactory medical treatment for it.

The chief presenting symptoms in order of frequency were as follows: vulval lump, pruritus, dysuria (burning on micturition), pain, ulceration, bleeding, discharge, lump in groin. Roughly 25 per cent had had symptoms for more than eighteen months which was, in about half the cases, due to delay in diagnosis by the physician. Clinical estimates of lymph node involvement were notoriously inaccurate and was wrong in about one-third of the cases, which "shows the clinical estimation of lymph node spread to possess an accuracy only a little better than the toss of a coin".

F. J. Browne

384. **Epidermoid Carcinoma of the Vulva. An Analysis of 238 Cases. Part II. Therapy and End Results.**

By T. H. Green, Jr., H. Ulfelder and J. V. Meigs. *Amer. J. Obstet. Gynec.*, **75**, 848–864. Apr. 1958. 9 tables. 7 figs. 4 refs.

The authors' opinion is that radiation therapy is not of any value in the primary treatment of cancer of the vulva. The local lesion is characterized by diffuse and multicentric foci of origin. In their series of 238 cases the presence of multiple independent areas of carcinoma was demonstrated in 47 (20 per cent). Hence a radical vulvectomy with wide margins is necessary so as to remove the entire vulval skin. Lymph nodes were involved in 60 per cent of the series, the involvement being bilateral in over half of these. There were no instances of deep pelvic node spread in the absence of superficial inguinal or femoral node involvement. The end results show that if adequately treated the disease is highly curable even if lymph nodes are involved. "Adequate treatment" is defined as a radical vulvectomy combined with bilateral superficial (inguinal, femoral and Cloquet's nodes), groin dissection preferably in continuity and in one stage. Of 69 cases given adequate treatment 42 were alive and well 5 years or more afterwards (61 per cent). Eighty-six per cent of the patients with negative nodes and 37 per cent of those with positive nodes were alive and well 5 years or more later. Though variables in the local lesion such as type, size and microscopic grade have a bearing on the incidence of nodal spread as well as on curability these are of far less significance than whether the patient received adequate treatment. In fact increasing histological grade and increasing size with the exception of very extensive lesions seem to have very little effect on curability if an adequate operation is done.

The operative technique is described in detail. In advanced cases with local extension beyond the vulva posterior exenteration should be considered.

F. J. Browne

385. **Vaginal Metastases from Adenocarcinoma of the Corpus Uteri.**

By F. N. Rutledge, S. K. Tan and G. H. Fletcher. *Amer. J. Obstet. Gynec.*, **75**, 167–174. Jan. 1958. 6 tables. 2 figs. 5 refs.

Because of the high incidence of vaginal metastases after total hysterectomy for cancer of the corpus uteri the authors advocate prophylactic combined intra-uterine and vaginal radiation followed by hysterectomy. In cases so treated the incidence of vaginal metastases after a 4-year follow-up was only 1·5 per cent compared with 20 per cent after hysterectomy alone. It is believed that the irradiation of the uterine growth, if not lethal for all tumour cells, damages them and renders them less likely to implant in the vagina, and that the irradiation of the vagina will destroy microscopic disease and obliterate potential metastatic channels, thus reducing the possibility of retrograde implants by milking action when the tumour is handled during operation.

F. J. Browne

386. **Report of a Malignant Melanoma of the Vestibule and External Urethral Meatus in a Woman Six Months Pregnant.**

By J. R. UPTON. *West. J. Surg. Obstet. Gynec.*, **66**, 199–203. July–Aug. 1958. 5 figs.

387. **Retroperitoneal Tumor of the Pelvis. Report of a Case.**

By R. D. REEKIE. *West. J. Surg. Obstet. Gynec.*, **66**, 204–209. July–Aug. 1958. 8 refs. 4 figs.

The author reports his first case of this condition among over 12,000 patients. Local removal was undertaken as a biopsy (taken from a vaginal extension) seemed to indicate a low grade of malignancy. After much pathological debate the diagnosis was fixed at "retroperitoneal lipofibrosarcoma". The patient, aged 23, has remained well for 3 years following operation.

D. C. A. Bevis

388. **Deciduosis of the Cervix Uteri.** (Deciduoza colului uterin.)

By G. TELEMAN and M. TELEMAN. *Obstet. Ginec. (Bucarest)*, 534–538. Nov.–Dec. 1957. 6 figs. 6 refs.

The authors distinguish between deciduosis of the cervix, which is a tumour peculiar to pregnancy, and the ordinary decidual reaction of the cervix. Deciduosis is a benign neoplastic condition, with widespread metaplasia of the endocervical glands and of the cells and vessels of the chorion. Clinically it resembles an early carcinoma, with a congested papilliferous surface that bleeds easily. Histological examination may be needed to exclude carcinoma. Deciduosis usually appears during the first trimester of pregnancy, when there are intense hormonal changes, and disappears after pregnancy.

Sylvia Lerer

389. **Histochemical Evaluation of Carcinoma in Situ of the Cervix.**

By R. E. L. NESBITT and A. A. STEIN. *Surg. Gynec. Obstet.*, **107**, 161–168. Aug. 1958. 9 figs. 8 refs.

This study constitutes a histological and cytochemical appraisal of cervical tissues obtained from 42 patients with carcinoma *in situ* admitted to the Albany Hospital, New York, during the 8-year period 1947–55. An attempt is made to find a reliable method of identification of the basement membrane, to find reliable histological criteria for diagnosis, and to evaluate the biological peculiarities of the lesion.

The periodic-acid-Schiff (PAS) staining technique proved to be simplest and most reliable for demonstrating the basement membrane. The PAS stainable cytoplasmic content (glycogen content) was also found useful in determining progress of epithelial maturation and metaplasia. In carcinoma *in situ* the entire thickness of the surface epithelium is made up of basal cells that are glycogen-free. The surface and alveolar columnar epithelia of the endocervix contain much glycogen, and the amount seems to be related to the hyperactivity of the glandular elements. Hyperplastic or anaplastic reserve cells appearing in the endocervix, however, do not take the stain and thus are readily distinguishable from the ordinary columnar epithelium or metaplastic squamous epithelium of the mature type.

Carcinoma *in situ* appears to result from atypical hyperplasia with failure of maturation in the basal cells of the exocervix or in the reserve cells of the endocervix. The change in the reserve cells is further complicated by failure in differentiation. The latter is commonly seen in carcinoma *in situ* and the authors regard the disease as one primarily of the endocervix.

Cervices with areas of carcinoma *in situ* of the basal cell type frequently showed variations in the morphological and staining patterns in contiguous areas of cervical epithelium. These commonly took the form of basal cell hyperactivity but occasionally also involved the prickle cell layer, producing an appearance reminiscent of Bowen's disease in other sites.

The relationship of the lesions to endogenous and exogenous hormones is discussed and it is interesting to note that of the 37 patients who had pan-hysterectomy performed 85 per cent showed marked stromal hyperplasia of the ovaries.

John P. Erskine

390. **Tetrazolium Staining in Cytology of the Uterine Cervix. Cytochemical Studies on Supravital Preparations of Benign and Malignant Origin.**

By P. M. MARCUSE. *Obstet. Gynec.*, **11**, 707–714. June 1958. 2 tables. 9 figs. 9 refs.

The histochemical demonstration of enzymatic activity in the cervix has been the subject of several recent investigations. The identification of specific enzymes and their localization are the main targets of these studies which are directed particularly at any detectable differences between normal and neoplastic tissue. The author's method, based on the reduction of neotetrazolium to coloured formazan, was applied to cervical scrapings from patients with cervical cancer, with benign lesions, and with normal cervices.

The results of modified tests indicate that reduction of the tetrazolium is not an expression of succinic dehydrogenase activity alone but that it depends also on the presence of endogenous reductase.

Analysis of results in the different groups revealed a preponderance of formazan deposits in the preparations derived from carcinomas. This high incidence of positive reactions in the malignant group seems related to the presence of active cells near the epithelial surface rather than to any specific quality of the cancer cells.

J. G. Dumoulin

391. **Mesonephric Carcinomas of the Ovary.**

By S. KAY and R. H. HOGE. *Surg. Gynec. Obstet.*, **107**, 84–94. July 1958. 18 figs. 7 refs.

The authors describe 9 mesonephric carcinomas of the ovary encountered during the past 7 years at the Medical College of Virginia. These comprise 13·6 per cent of the 66 ovarian carcinomas submitted to the laboratory during the same period.

The tumours were presumed to be of mesonephric origin because of their resemblance to neoplasms arising in other parts of the female genital tract where Gartner's duct can be implicated on anatomical grounds. Four of the tumours showed areas of typical hypernephroma.

The tumours were generally cystic with solid areas, but the macroscopic appearance was not distinctive. Papillary structures were a feature in some, and a few of the growths showed mucoid substance extruding from the cut surface. The microscopic appearances varied from field to field. Typical hypernephroid carcinoma was present in large areas, with transitional changes to simple tubules lined by epithelial cells with little or no vacuolated cytoplasm. Some tubules showed dichotomous branching reminiscent of the developing mesonephron. Typical glomerulus-like structures were not seen. The resemblance of tubules to the Wolffian or mesonephric apparatus was noted in parts of some of the tumours.

Treatment was generally by total hysterectomy with removal of the appendages, followed by X-ray therapy. Follow-up examinations in general have been too brief but it is known that four patients died of the tumours. The neoplasms are malignant and the prognosis is grave, particularly if capsular invasion and adhesion to adjacent structures is present.

John P. Erskine

392. **The Argument Against Preoperative Radium for Endometrial Cancer.**

By C. E. McLennan. *West. J. Surg. Obstet. Gynec.*, **66**, 193–198. July–Aug. 1958. 19 refs.

The use of intracavitary radium followed some weeks later by hysterectomy is a common method of treatment for endometrial carcinoma in some parts of America. It seems to be a relic of the times when no clear distinction was drawn between malignancy of the cervix and of the body of the uterus. The author, from Stanford University, deplores this treatment and after reviewing the literature describes his experience; 105 women were treated between 1940 and 1952, 55 had a total hysterectomy with bilateral salpingo-oöphorectomy and five years later 52 were alive and well. Twenty-three had radium alone and here the survival was 12. A further 27 patients had pre-operative radiation and 24 survived five years. He concludes that the strongest argument against this therapy is the fact that no convincing argument for it has ever existed.

D. C. A. Bevis

OPERATIONS

393. **Vasopressin as a Hemostatic in Gynecological Surgery. A Preliminary Report.**

By T. F. Dillon, B. E. Marbury, R. W. Bonsnes, G. Douglas and V. Du Vigneaud. *Obstet. Gynec.*, **11**, 363–371. Apr. 1958. 4 tables, 5 figs. 27 refs.

Vasopressin, a purified posterior pituitary hormone, causes contraction and vasoconstriction in the non-pregnant uterine muscle. The authors report on its use as a haemostatic in certain gynaecological operations such as myomectomy, unification of bicornuate uteri, and tuboplastic operations. Vasopressin was used only in patients under 40 years of age with a normal cardiovascular system because constriction of the coronary arteries has been attributed to it.

Four units were selected as the maximum dosage and were diluted in 20 ml. of saline. Injection was made direct into the uterine muscle which blanches in a few seconds, the effect lasting for 15 to 20 minutes.

Blood loss was markedly reduced and there were no complications in the series of 20 operations reported on.

J. G. Dumoulin

394. **Some Contributions to the Tubal Re-permeability by Surgical Procedure Associated with Therapeutic Hydrocortisone.** (Contributii la studiul repermiabilizari tubare prin procedee chirurgicale asociate terapeutic cu hidrocortisone.)

By I. Parhon, E. Petrescu, I. Moldoveanu, E. Bogatila and P. Cana. *Obstet. Ginec.* (*Bucarest*), 538–543. Nov.–Dec. 1957. 6 refs.

After operations for tubal obstruction closure of the new stoma or at the site of uterine implantation may occur. In 48 cases clinical and radiological follow-up showed failure in 70 per cent of cases, so the authors have sought to improve their results by using hydrocortisone and streptomycin as adjuvants to the surgical treatment. They describe two procedures, the intraperitoneal method of injecting these substances into the new stoma of a reconstituted tube, and the second method of post-operative injection through the uterus.

They have explored the patency of the reconstructed tube: (1) by injecting 50 mg. of hydrocortisone and 1 g. of streptomycin in 10 ml. of 1 per cent novocaine through the Nelaton tube, and (2) in the ascending test they injected the same solution through the uterus. This test was repeated several times at 2 to 3 day intervals. In the last investigation they also used an opaque medium for hysterosalpingography. They have treated 8 cases, and 7 were successful.

The authors consider that the hydrocortisone not only inhibits local inflammatory reaction but that it also has a general action through the central nervous system, by interrupting the nocive actions of a complex enzyme on the tissues.

Sylvia Lerer

395. **The Prevention of Post-Operative Adhesions.** (Die Verhütung postoperativer Adhäsionen.)

By K. Niedner. *Zbl. Gynäk.*, **80**, 932–938. June 14, 1958. 3 figs.

Trauma to the peritoneal endothelium is followed by the appearance of a fluid which coagulates and seals the surface with a layer of collagen, which later undergoes organization. On this mechanism is based safe seroserous intestinal suturing. During abdominal operations, however, trauma to the peritoneal surfaces results in the formation of additional undesirable adhesions. Much can be done towards their prevention by careful surgical technique. This includes avoidance of contamination of the peritoneal cavity, covering the abdominal skin com-

pletely with sterile towels, gentle handling of the wound edges, protection of the intestine with warm saline compresses, careful attention to haemostasis, the use of suction apparatus rather than traumatizing swabs, sharp and light instruments for dissection, and the finest possible suture material. In spite of these precautions there remains in some patients a risk of formation of undesirable adhesions.

During the five years preceding this report the author has therefore been using a peritoneal lubricating material consisting of polygalacturonic acid in which the acid groups have been esterified with methanol, in a 1·5 per cent isotonic colloidal solution ("Hämophobin").

He reports the results of experiments on 50 guinea-pigs in which the peritoneum was damaged by one of three methods: removal of strips of peritoneum; scarification; or cauterization. In 50 per cent of the animals 0·4 ml. of "Hämophobin" was instilled in the peritoneal cavity before closure of the incision. The animals were subsequently killed and it was found that in the treated group adhesions formed only in two, in which strips of peritoneum had been removed, whereas in the control group 4 animals died from purulent peritonitis and 6 developed peritoneal adhesions.

For the avoidance of post-operative adhesions the author recommends meticulous surgical technique and "Hämophobin" which he used with satisfactory results in 184 abdominal operations in the human.

Bruce Eton

UROLOGY

396. **Fistulae of the Urinary Tract in the Female: A Proposed Classification.**

By E. L. F. McConnachie. *S. Afr. med. J.*, **32**, 524–527. May 17, 1958. 4 tables.

The author has dealt with over 300 cases of urinary tract fistula in 8 years. He feels that classification is necessary so that reports by various authors may be compared. Fistulae seen in South Africa, India, Egypt, China and Asia Minor are due chiefly to inadequate obstetrical facilities. Those seen in the United Kingdom and Western Europe are generally small and clean, and thus could not be compared on the basis of results. A classification is submitted. The grade of fistula depends on whether normal healthy tissues and sphincters are present, together with easy access. Type of fistula is dependent upon size. There are 5 grades (1–5), and 4 types (A–D). The aetiology may be added to the end of the formula as a point of scientific interest, e.g., VVF 11 B (parturition). In 298 cases complete control of urinary function was achieved in 64·6 per cent. Based only on fistula closure the cure rate was 79·5 per cent. The classification has been of value in helping to select the type of repair and in making the prognosis from a clinical aspect.

L. J. Abramowitz

397. **Urethral Diverticula: An Assay of 121 Cases.**

By H. J. Davis and R. W. TeLinde. *J. Urol.*, **80**, 34–39. July 1958. 6 figs. 5 refs.

One hundred and twenty-one cases are reported, 50 of whom were discovered in the year prior to publication. The theories of causation are discussed. Only one had a congenital cause—an ectopic ureter. Twenty-eight of the patients were nulliparous, and only two were under the age of 15. The great majority of patients were between the ages of 20 and 40.

The common symptoms were frequency, dysuria, a suburethral mass and pus on digital stripping. The diverticulum can easily be missed on cystoscopy. Urethroscopy is always advisable and the diagnosis should be confirmed by urethrography. It is important to bear in mind that a diverticulum may be a compound one, and that also diverticula may be multiple. Surgical treatment gives satisfactory results.

J. H. Carver

398. **Primary Carcinoma of the Female Urethra.** (Das primäre Urethralkarzinom bei der Frau.)

By G. Topp. *Zbl. Gynäk.*, **80**, 788–801. May 17, 1958. 2 tables. 32 refs.

The author reviews a series of 15 cases of carcinoma of the female urethra encountered between 1937 and 1957. Ten of the patients were over 60 years of age. The inguinal lymph nodes were enlarged in 4. In 2 cases the tumour was an adenocarcinomatous polyp. The other 13 were squamous-cell carcinomata. Several of these had the appearance of a urethral caruncle.

The treatment consisted of local excision, followed by radium and X-ray therapy. In 8 cases the inguinal lymph nodes were also treated with X-rays. The author claims that such combined treatment gives the best results. The follow-up period, however, is still too short: 9 patients were free from recurrence after two years and 2 of these after five years.

[In this country surgical treatment of carcinoma of the urethra is probably more radical than that outlined by the author.]

Bruce Eton

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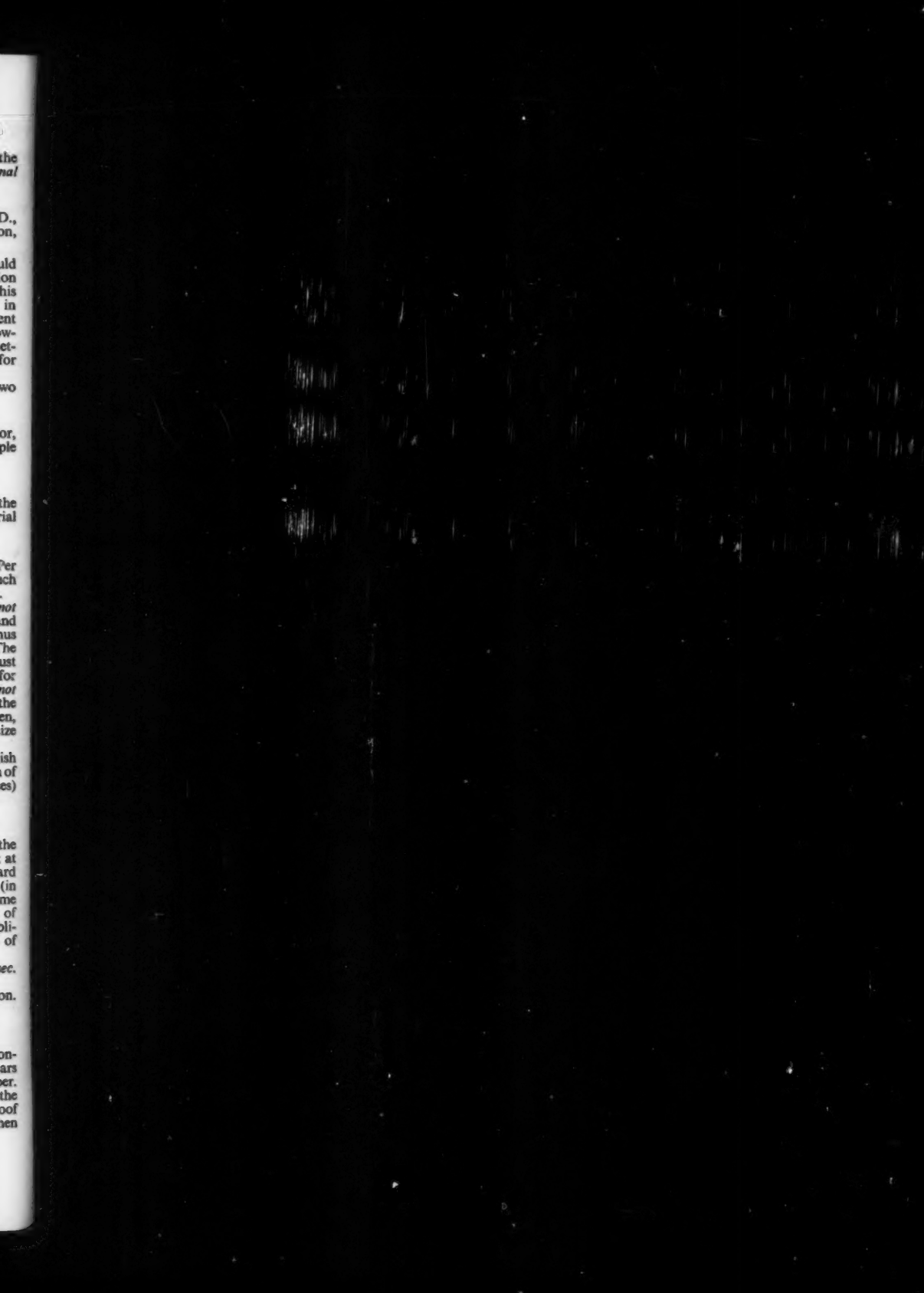

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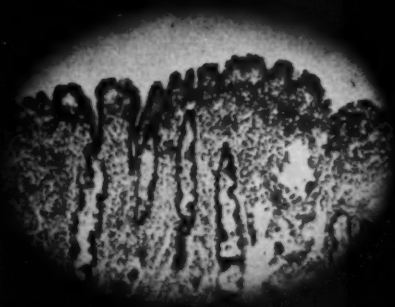

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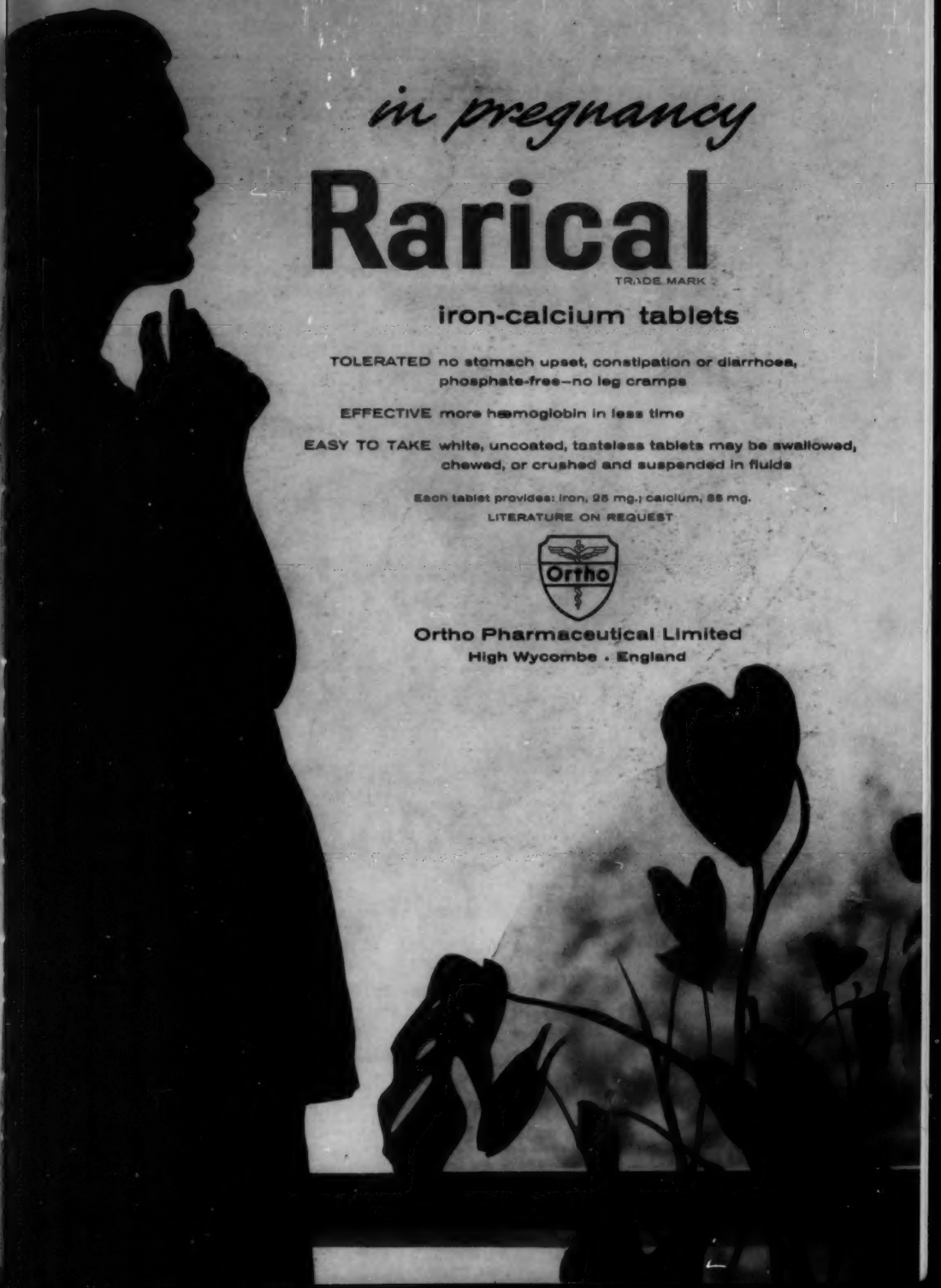

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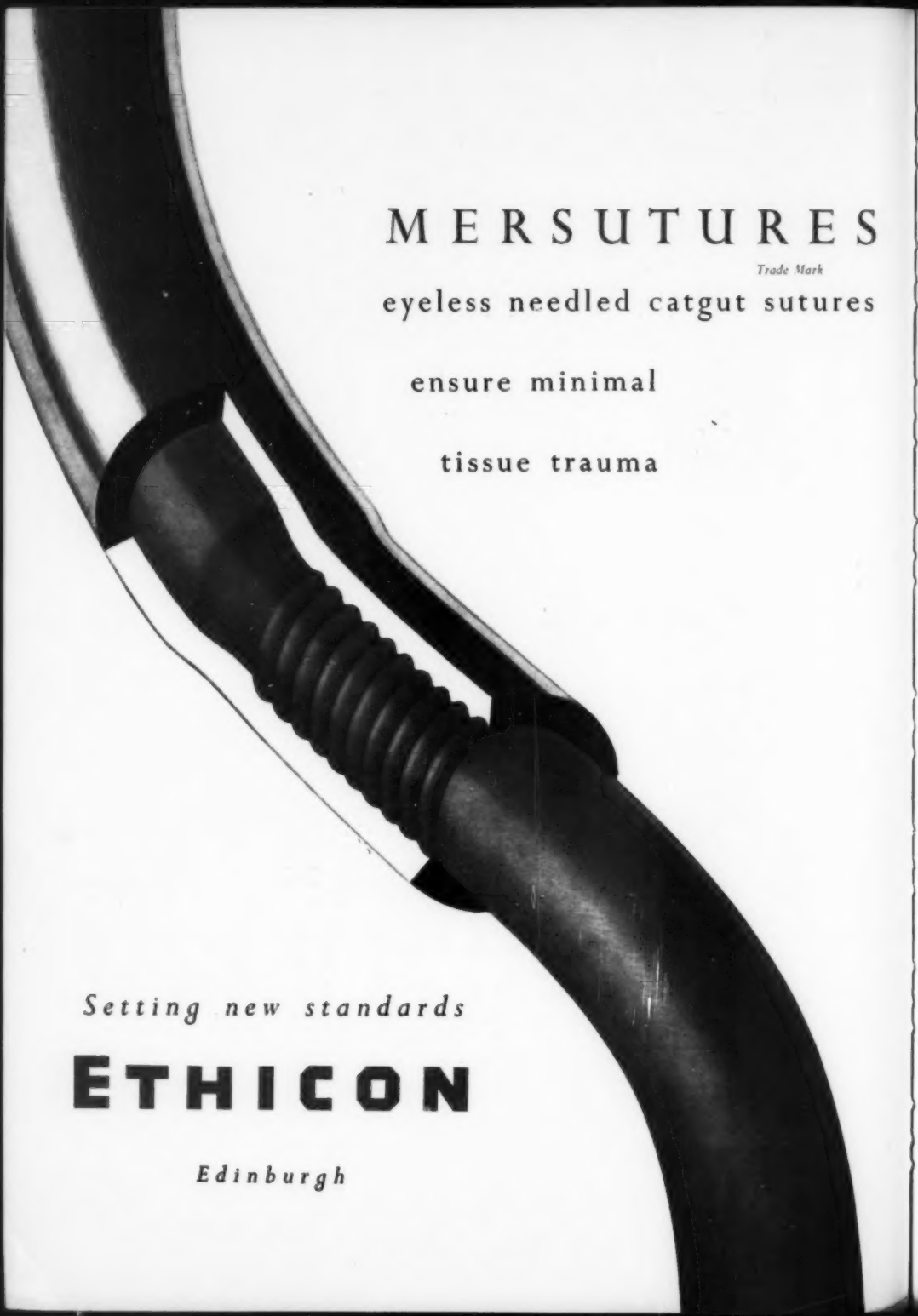

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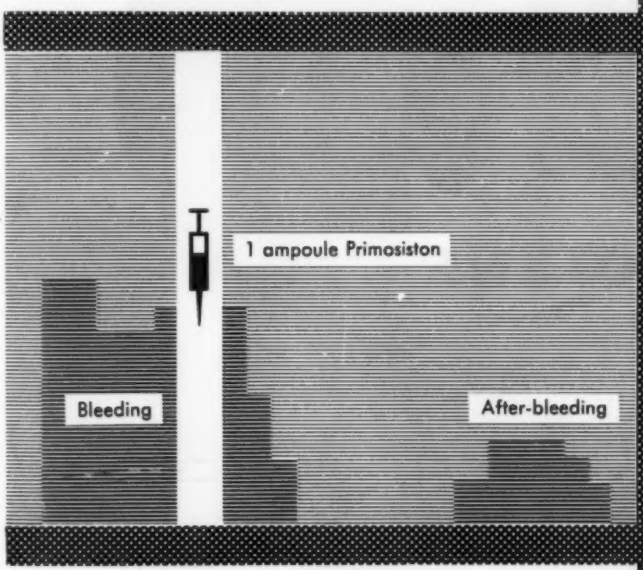

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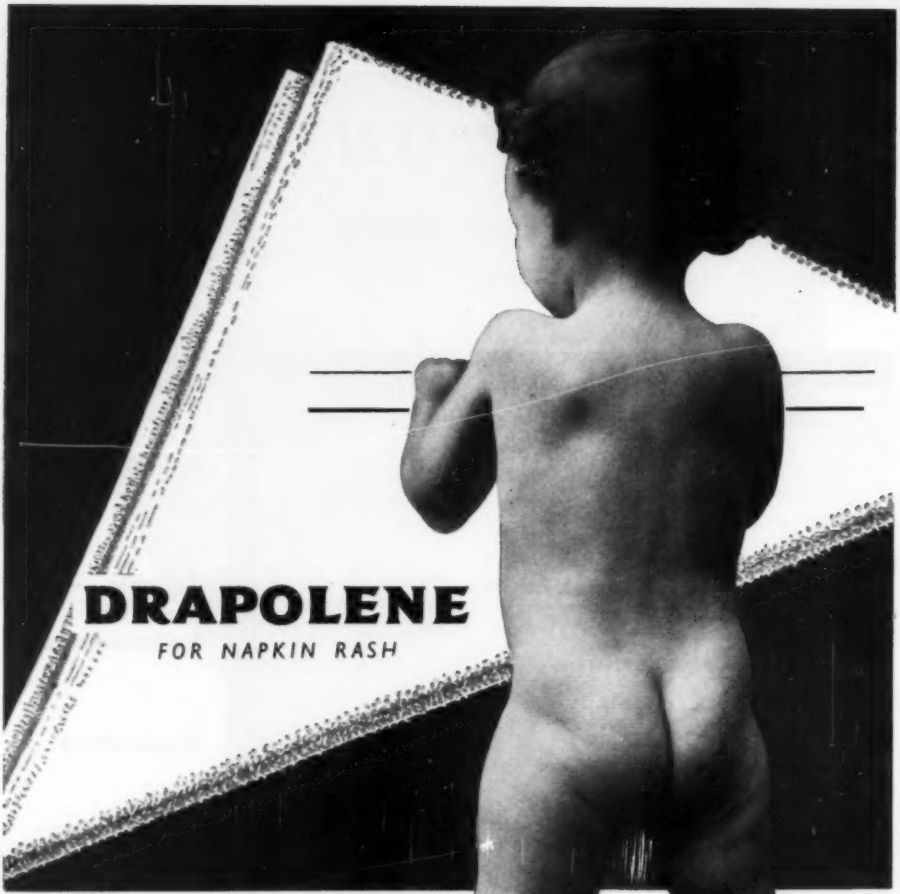

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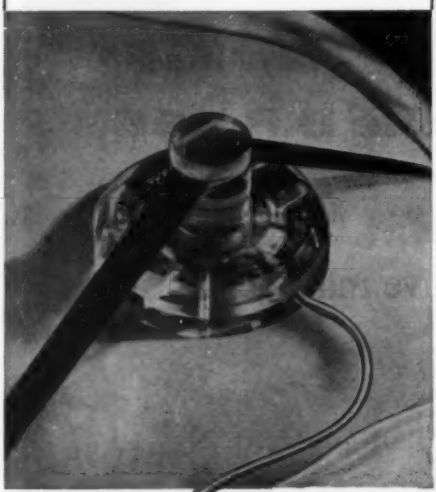

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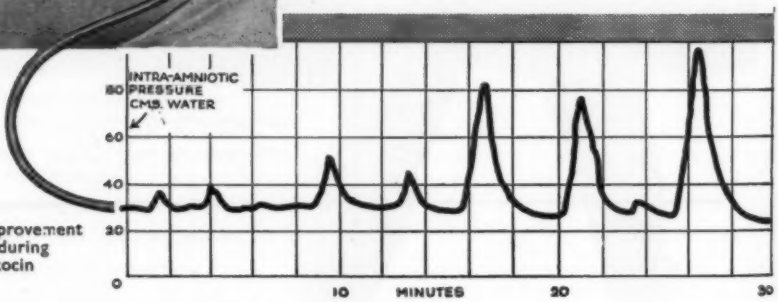

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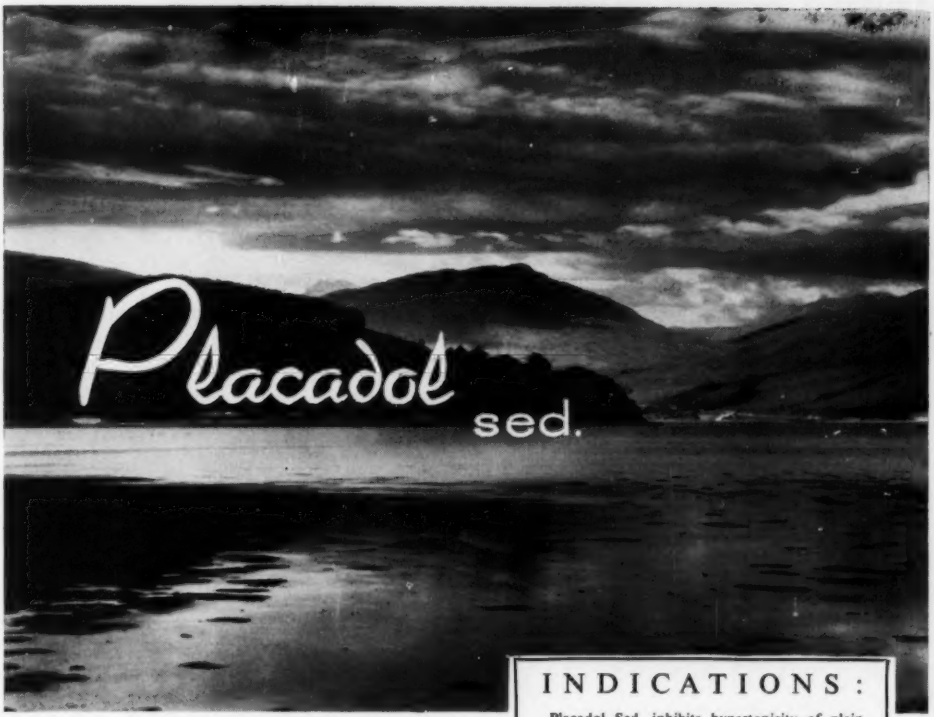

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